Onkološki Inštitut
Institute of Oncology
Ljubljana 80 let years

KATEDRA ZA ONKOLOGIJO
SEKCIJA ZA INTERNISTIČNO ONKOLOGIJO

Slovensko Zdravniško Društvo

#1. SUMMER SCHOOL IN MEDICAL ONCOLOGY

Part 1 – Tuesday (3.9.) & Wednesday (4.9.)

LJUBLJANA
3-6. SEPTEMBER 2019

Strokovni odbor:
izr. prof. dr. Janja Ocvirk, dr.med.
doc. dr. Martina Reberšek, dr.med.
dr. Tanja Mesti, dr.med.
Marko Boc, dr.med.

Organizacijski odbor:
izr. prof. dr. Janja Ocvirk, dr.med.
doc. dr. Martina Reberšek, dr.med.
dr. Tanja Mesti, dr.med.
Marko Boc, dr.med.
ga. Lidija Kristan

Uredniki zbornika:
Marko Boc, dr.med.
doc. dr. Martina Reberšek, dr.med.
izr. prof. dr. Janja Ocvirk, dr.med.
dr. Tanja Mesti, dr.med.

Organizator in izdajatelj (založnik):
Onkološki inštitut Ljubljana
Sekcija za internistično onkologijo
Katedra za onkologijo

Ljubljana, september 2019

AGENDA & INDEX

Tuesday, September 3

10:30-11:00	Registration of participants	
Part 1	***Moderators: dr. Dobrila, dr. Boc***	
11:00-11:30	Neoadjuvant and Adjuvant treatment strategies for gastric cancer (dr. Boc)	
11:30-12:15	Systemic treatment of metastatic gastric cancer (dr. Dobrila)	
12:15-12:35	Neoadjuvant and Adjuvant treatment strategies for pancreatic cancer (dr. Mesti)	
12:35-13:15	Systemic treatment of metastatic pancreatic cancer (dr. Mesti)	
13:15-13:30	Discussion	
13:30-14:30	Lunch break	
Part 2	***Moderators: dr. Pleština, dr. Hlebanja***	
14:30-14:50	Satellite symposium	
14:50-15:20	Systemic treatment of biliary tract cancer (dr. Reberšek)	
15:20-15:40	Systemic treatment strategies for HCC (dr. Mesti)	
15:40-16:10	Adjuvant treatment strategies for colorectal cancer (dr. Ignjatović, dr. Ocvirk)	
16:10-16:55	Systemic treatment of metastatic colorectal cancer (dr. Pleština)	
16:55-17:10	Discussion	

Wednesday, September 4

Part 1	***Moderators: dr. Radosavljevič, dr. Grašič Kuhar***	
8:30-9:15	Neoadjuvant and Adjuvant treatment strategies for lung cancer (dr. Radosavljevič)	
9:15-10:00	Systemic treatment of metastatic lung cancer (dr. Zarić)	
10:00-10:45	Systemic treatment of head and neck cancer (dr. Grašič Kuhar)	
10:45-11:00	Break	
11:00-11:30	Systemic treatment of patients with unknown primary tumor (dr. Matos)	
11:30-11:45	Systemic treatment of germinal tumors (dr. Škrbinc)	
11:45-12:15	Discussion	
12:15-12:45	Satellite symposium (Roche)	
12:45-13:45	"First line treatment of metastatic NSCLC" (*dr. Maximilian J. Hochmair*)	
13:45-14:30	Lunch break	
Part 2	***Moderators: dr. Belev, dr. Šeruga***	
14:30-15:15	Systemic treatment of prostate cancer (dr. Belev)	
15:15-16:00	Systemic treatment of RCC (dr. Šeruga)	
16:00-16:15	Break	
16:15-16:45	The systemic treatment of the bladder cancer (dr. Mencinger)	
16:45-17:15	The palliative care - when to start and how to lead the patient and the patients family through the process (dr. Ebert Moltara)	
17:15-18:15	Interesting cases from audience	

PERI-OPERATIVE TREATMENT OF GASTRIC CANCER

Marko Boc, dr.med.
Sector of medical oncology
Institute of Oncology Ljubljana
SLOVENIA

Ljubljana, 3-6. september 2019

Summary

- Peri-operative chemotherapy (pre- and post-operative) is standard of care for unmetastatic resectable gastric cancer ≥ Stage IB **(ESMO: I,A):**
  - Peri-operative chemotherapy comprises a platinum compaund and a fluoropyrimidine,
  - Addition of epirubicine is optional (toxicity), strongest evidence for cisplatin/fluorouracil ± epirubicine,
- Taxanes improve peri-operative chemoterapy response and improve survival outcomes trough better response.
- For patients ≥ Stage IB gastric cancer who have undergone surgery without administration of pre-operative chemotherapy or post-operative CRT, **adjuvant chemotherapy** is recommended (**ESMO: I,A):**
  - S-1 (**1,A)** and XELOX in Asian pupulation
  - 6% absolute benefit for 5-FU based chemotherapy, [HR 0.82 (0.76-0.90), p<.0001] **(ESMO: 1,A).**

Summary

- Post-operative CTX intensification did not improve outcomes!
- Since capecitabine avoids the need for an central venous access device, and is non-inferior to 5-FU in the advanced disease setting, capecitabine-containing regimens can also be suggested in the peri-operative setting **(ESMO: IV,C).**
- For patients with ≥Stage IB gastric cancer who have undergone surgery without administration of preoperative chemotherapy, **postoperative chemoradiotherapy (CRT) (ESMO: I,A).**
- For patients having undergone preoperative chemotherapy, the addition of postoperative radiotherapy (RT) has no added benefit.

PANCREATIC ADENOCARCINOMA

TANJA MESTI, MD, PHD

INSTITUTE OF ONCOLOGY LJUBLJANA

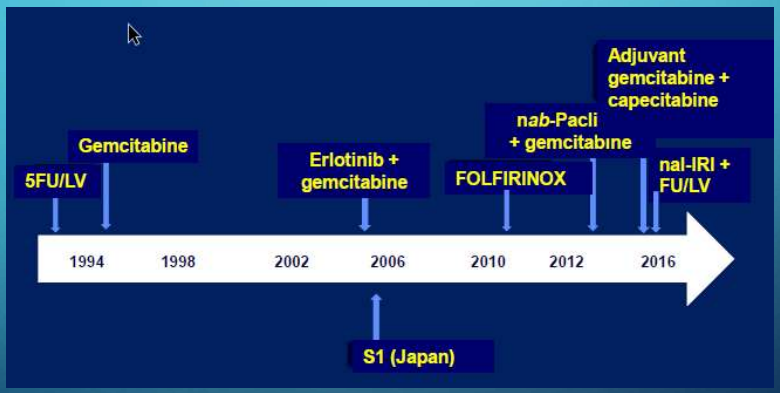
ADJUVANT TREATMENT

- Adjuvant ChT > DFS & OS
- Adjuvant ChT > operation alone
- m- FOLFIRINOX the best, but the most toxic option
- m- FOLFIRINOX - PS (0-1)

NEOADJUVANT TREATMENT

- Limited data
- Best recommended (m)FOLFIRINOX ± RT or
  gemcitabin + nab-paklitaksel ± RT
- Tertiary care centers
- **Multidisciplinary planning**

SYSTEMIC TREATMENT FOR METASTATIC DISEASE



Van Custeem E. ESMO Academy 2017

CONCLUSIONS

- Initially CT th/abd
- CA 19-9
- **Multidisciplinary approach**
- Treatment according to the guidelines
- Pts preferences, tumour burden, comorbidities

CONCLUSIONS

- Inclusion in the clinical studies if possible
- Systemic treatment for advanced or metastatic pancreatic adenocarcinoma < symptoms and tumour burden and > survival
- **GOOD PALLIATIVE CARE – EARLY**

Systemic treatment of biliary tract cancers

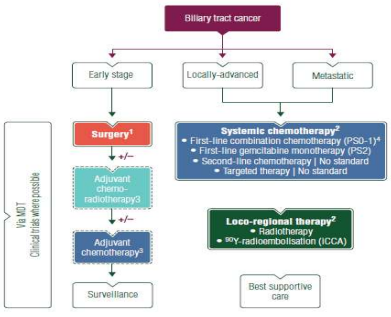
1st Summer school in medical oncology - standards and open questions

ASSIST.PROF.MARTINA REBERŠEK, MD

DEPARTMENT OF MEDICAL ONCOLOGY

INSTITUTE OF ONCOLOGY LJUBLJANA

J. W. Valle, et al. On behalf of the ESMO Guidelines Committee Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up- 2016



[1] Special considerations:
- Need for pre-operative biliary drainage
- Avoid percutaneous biopsy in resectable disease
- Assess Future Liver Remnant
- Assess need for Portal Vein Embolisation
- Neoadjuvant approach (selected cases)
- Completion surgery for incidental gallbladder cancer of T-stage T1b and above

[2] Option of salvage surgery should be considered in responding patients with initially inoperable disease
[3] Level of recommendation IV,C
[4] Cisplatin and gemcitabine [category IA], other gemcitabine-based combination [category IIB]

Figure 1. Algorithm for the management of patients with biliary tract cancer. MDT, multidisciplinary team; PS, performance status; iCCA, intrahepatic cholangiocarcinoma.

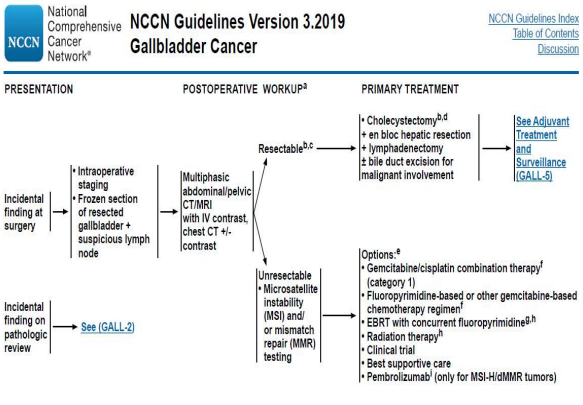
Annals of Oncology 27 (Supplement 5): v28–v37, 2016 doi:10.1093/annonc/mdw324

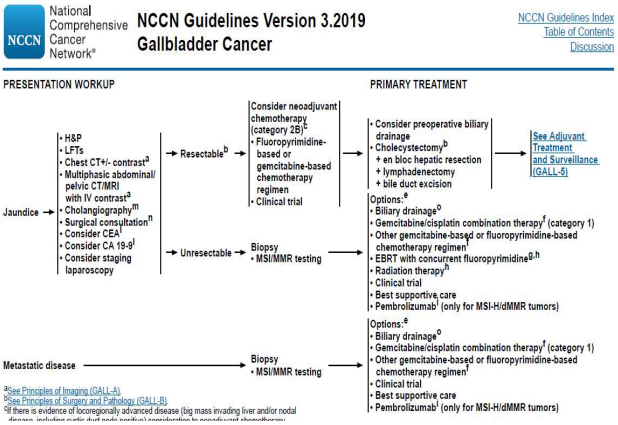
NCCN and ESMO guidelines for adjuvant systemic treatment

Cancer Type	Guideline: NCCN[40]	Guideline: ESMO[41]
Gallbladder		
R0/N0 or CIS at margin	Observation or FU CRT or FU- or gemcitabine-based CT or Clinical trial	± adjuvant chemotherapy, radiation or CRT after risk-benefit assessment
R1 or R2 or node positive	FU CRT then FU- or gemcitabine-based CT or FU- or gemcitabine-based CT ± FU CRT or Clinical trial	
Intrahepatic cholangiocarcinoma		
R0	Observation or Clinical trial or FU- or gemcitabine-based CT	± adjuvant chemotherapy, radiation, or CRT after risk-benefit assessment
R1 or node positive	Clinical trial or FU CRT or FU- or gemcitabine-based CT ± FU CRT	
R2	Clinical trial or FU- or gemcitabine-based CT ± FU CRT or Locoregional therapy or Best supportive care	
Extrahepatic cholangiocarcinoma		
R0, N0 or CIS at margin	Observation or FU CRT or FU- or gemcitabine-based CT or Clinical trial	± adjuvant chemotherapy, radiation or CRT after risk-benefit assessment
R1 or R2 or node positive	FU CRT + FU- or gemcitabine-based CRT or FU- or gemcitabine-based CRT ± FU CRT or Clinical trial	

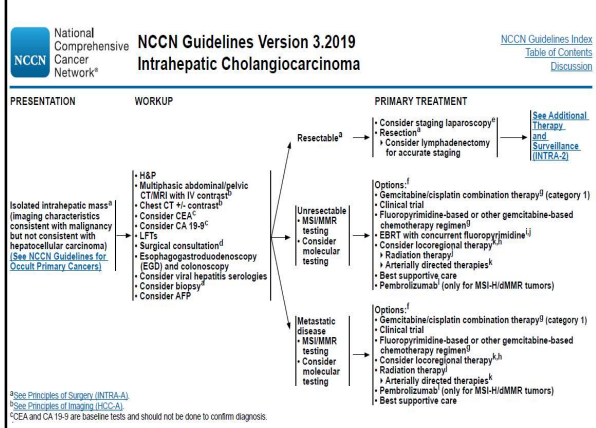
Horgan AM,Knox JJ.Adjuvant Therapy for BiliaryTract Cancers. Volume 14 / Issue 12 / December 2018 Journal of Oncology Practice, 2018; 14:12.

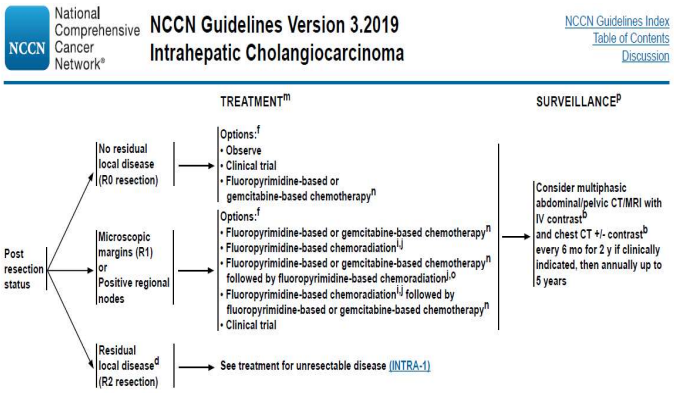
NCCN: Gallbladder cancer



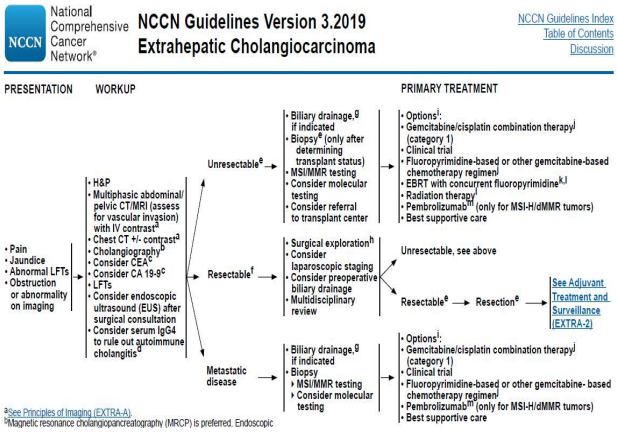


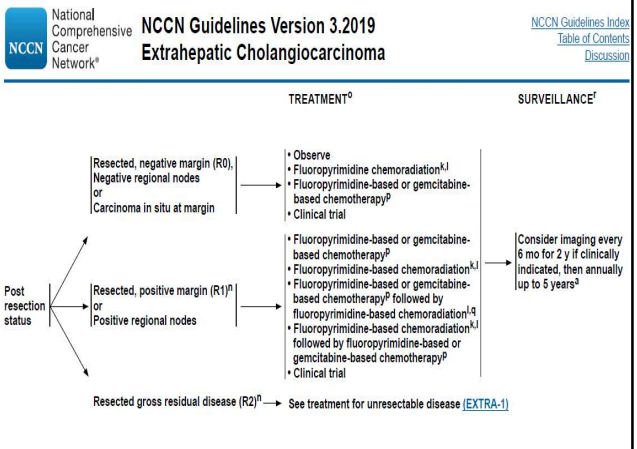
NCCN: Intrahepatic cholangiocarcinoma





NCCN: Extrahepatic cholangiocarcinoma





Conclusions(1)

- rare cancers
- poor prognosis
- important diagnostic procedures
- surgical treatment first

Conclusions (2)- systemic treatment

• **Neo- adjuvant therapy:** no standards

• **Adjuvant therapy:**

- capecitabine monotherapy

- role of radiation therapy in combination with systemic treatment- the need of prospective randomized clinical phase III trials

• **Metastatic disease:**

- 1st line: gemcitabine + cisplatin (PS ECOG 0-1), gemcitabine mono (PS ECOG 2)

- 2nd line: no standard therapy

- targeted therapy: no standards

- **Immunotherapy: MSI- H**

HCC – systemic treatment strategies

TANJA MESTI, MD, PHD

INSTITUTE OF ONCOLOGY LJUBLJANA

Key Takeaways

- Sorafenib and regorafenib are the only agents approved for advanced HCC
  - Both are multikinase inhibitors with prominent antiangiogenic effects
  - Sorafenib is approved for first-line treatment
  - Regorafenib is approved for second-line treatment after sorafenib failure or intolerance
- In a head-to-head phase III trial, lenvatinib was shown to be noninferior to sorafenib and may be considered an alternative to sorafenib, particularly in patients with intolerance
- Important to recognize the class-wide side effects of these agents (eg, hand-foot skin reaction, hypertension, diarrhea, weight loss) and employ timely interventions to optimize treatment outcomes

i3Health

Landscape-Second line therapy for HCC

		Total N	PFS benefit	OS benefit	RR
CHECKMATE040 (SINGLE ARM)	Nivolumab*	154	NA	NA median OS ≈15 mo*	14%
RESOURCE	Regorafenib* v placebo	573 (2:1)	+1.6 mo HR 0·46 (0.37-0.56); p<0·0001	+2.8 mo HR 0.63 (0.50-0.79) p<0.0001)	11%
CELESTIAL**	Cabozantinib v placebo	707 (2:1)	+3.3 mo HR=0.44 [0.36-0.52]; *P* < 0.001	+2.2 mo HR=0.76 (0.63-0.92) P = 0.0049	4%
REACH1	Ramucirumab v placebo	565	+0.7mo HR 0.63 [0.52-0.75]; p<0.0001	NO	7%
REACH 2 (AFP≥400)	**Ramucirumab v placebo**	**292 (2:1)**	**+1.2 mo HR 0.452 (0.339, 0.603) p< 0.0001**	**+1.2 mo HR 0.71 (0.531, 0.949); p=0.0199**	**4.6%**
Pooled REACH 1 / 2 (AFP≥400 subgroup)	*Ramucirumab v placebo*	*542*	*NA*	*+3.1 mo HR 0.694 (0.571, 0.842) P=0.0002*	*NA*

PRESENTED AT: 2018 ASCO ANNUAL MEETING

*FDA approved
** included 2nd and 3rd line; 2nd line update: Kelley, et al. Abstr #4088 ASCO 2018

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ADJUVANT TREATMENT STRATEGIES FOR COLORECTAL CANCER

1st Summer School in Medical Oncology

3. – 6. September, Ljubljana, Slovenia

Marija Ignjatović,MD

ADJ.ChT IN CRC

- ❑ **Start 4 to 8 weeks after operation**
- ❑ **Stage II**
  - ✓ **Can not be considered as a SOC for all patients**
  - ✓ **HR, pMMR: capecitabine** or 5FU **for 6 months**
  - ✓ **HR, dMMR: just <u>for very selected patients</u>, XELOX for 3 months or FOLFOX for 6 months**
- ❑ **Stage III**
  - ✓ **SOC**
  - ✓ **LR, XELOX for 3 months**
  - ✓ **HR, XELOX/FOLFOX for 6 months**

Neoadjuvant and adjuvant treatment strategies for lung cancer

Davorin Radosavljevic

Institute for Oncology and Radiology of Serbia

Belgrade

„1st Summer School in Medical Oncology - Standards and Open Question“,

September 3-6th 2019, Ljubljana, Institute of Oncology

conclusions

- adjuvant chemotherapy is established for stage II and III resected NSCLC with sustained benefit
- the regimen with most evidence is cisplatin vinorelbine although the accepted schedule differs from JBR.10 and ANITA trials
- stage IB tumours can be considered for adjuvant chemotherapy if >/= 4cm although evidence is from unplanned, retrospective analyses (CALGB 9633 and JBR.10)
- selected older patients (70+) tolerate chemotherapy with acceptable toxicity but limited evidence for elderly and very elderly (75+, 80+)
- further major improvements with chemotherapy alone are unlikely (pemetrexed?)
- research will be focused on better discrimination of high versus low risk patients, predictive factors and more targeted therapies

Conclusions

- The local/regionally advanced setting is rapidly evolving with the addition of immunotherapy
- The new standard of care in patients with unresectable disease: concurrent chemoradiation, followed by one year of durvalumab
- Future studies, exploring the role of replacing chemotherapy with immunotherapy in unresectable disease and adding adjuvant or neoadjuvant immunotherapy in resectable disease, may further reshape our standard practice

Institute for Pulmonary Diseases of Vojvodina
Faculty of Medicine, University of Novi Sad
Serbia

Systemic treatment of metastatic lung cancer

Assist. Prof dr Bojan Zarić, MD, PhD
Head, Department for diagnostics and treatment of lung cancer
Head, Clinical Trials Unit

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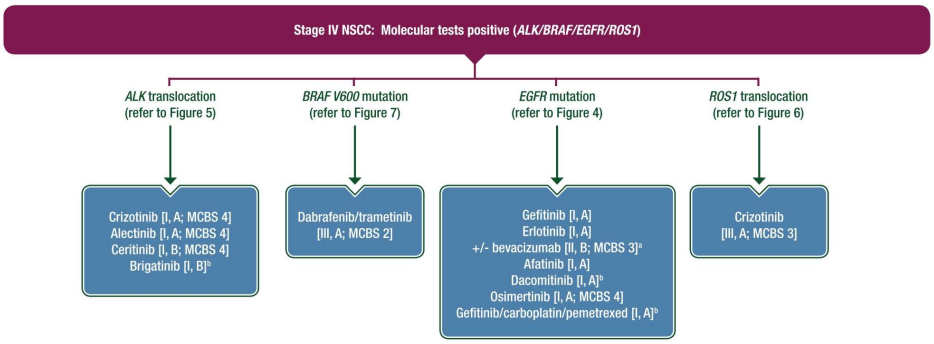
Oncogene driven lung cancer treatment in first line



Oncogene driven lung cancer treatment beyond first line

- Based on molecular profiling and determination of resistance mechanism,
- Should be tailored to target secondary mutation (if any), otherwise RCT or standard platinum based doublet,
- Adequate sequencing remains to be determined.

Treatment of metastatic lung cancer without driver mutations in first line

- TPS ≥ 50% (≥1%) - pembrolizumab monotherapy,
- High TMB – Nivolumab/Ipilimumab,
- Any expression of PD-L1 – IO/Chemo combo, standard platinum based therapy.

Treatment of metastatic lung cancer without driver mutations beyond first line

- Immunotherapy if not given in first line (regardless of PD-L1 expression,
- RCT,
- Docetaxel mono or any other available (platinum) based chemotherapy.

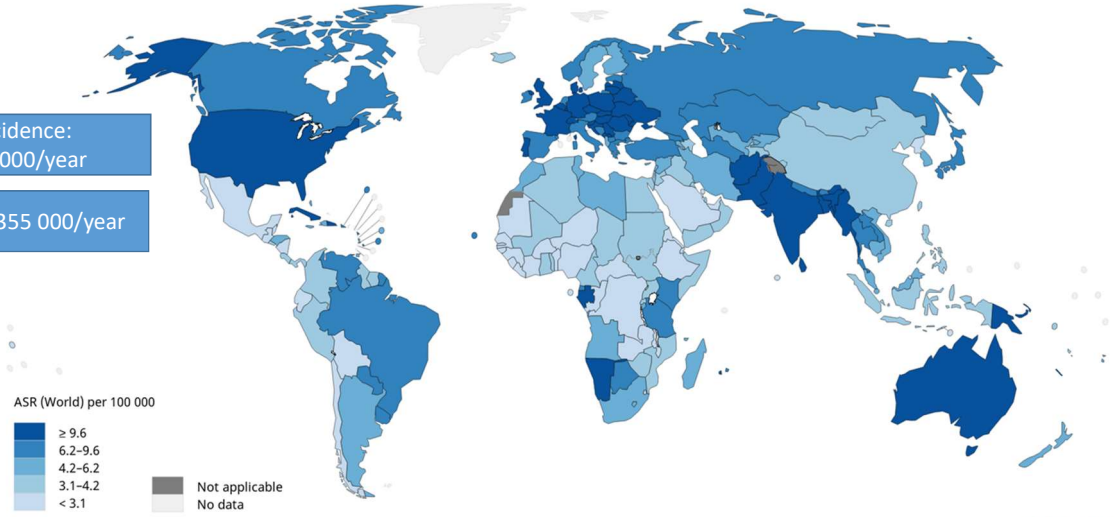
Systemic treatment of head and neck tumors

Assist. Prof. Cvetka Grašič Kuhar, MD, PhD
Institute of Oncology Ljubljana, Department of Medical Oncology

lip, oral cavity, oropharynx, larynx, hypopharynx

Accessed 15.8.2019

Estimated age-standardized incidence rates (World) in 2018, both sexes, all ages



Incidence: 640 000/year

Deaths: 355 000/year

Data source: GLOBOCAN 2018
Graph production: IARC (http://gco.iarc.fr/today)
World Health Organization

Etiology, risk factors

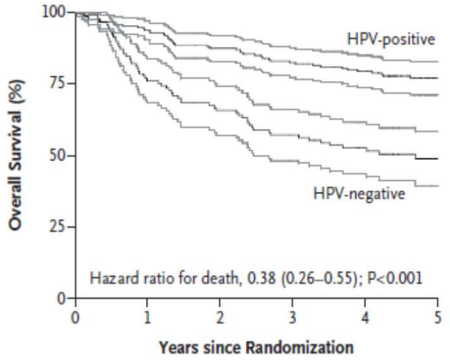
- Tobacco
- Alcohol
- HPV
- EBV
- Chewing of betel leafs
- UV-exposure (lips)
- Poor oral/dental hygiene/mechanical irritation
- Occupational hazards: wood dust, leather industry, nickel, azbestos
- Gastroesophageal reflux disease
- Genetic syndrome (i.e. Fanconi anemia)

HPV+ vs. HPV- oropharyngeal carcinoma

	HPV+	HPV-
Localisation	Tonsil, Base of toungue	All localizations
Histology	nonkeratinizing, basaloid, high grade	keratinising
Age Soc econ status Performance status	53–57 years Good Better	57–64 years, Lower Lower
Gender	3:1 for men	3:1 for men
T stage N stage	Low T (Tx, T1-2) high N stage, cystic cervical nodes	High T stage High N stage, noncystic
Molecular char. PD-L1 overexpression DNA metilation	PI3KCA mutated 49-70% more	p53 mutated 29-34% less
Risk factors	Sexual behaviour, associated with HIV in anogenital HPV, less tobacco	Tobacco, alcohol
3-year risk for metastases	9-11 %	14-15 %
3- and 8-year OS of stage III, IV	82 and 71 %	57 and 30 %

HPV is a prognostic factor

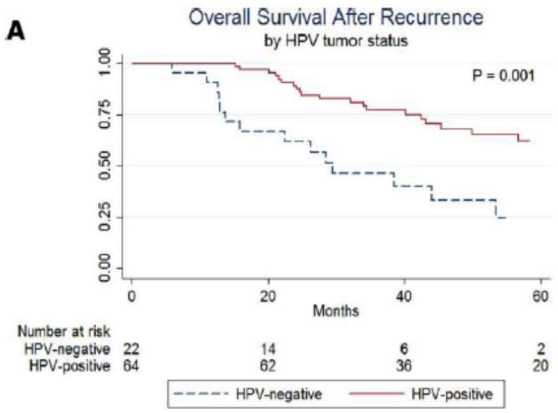
Primary



No. at Risk						
HPV-positive	206	193	179	165	151	73
HPV-negative	117	89	76	65	51	22

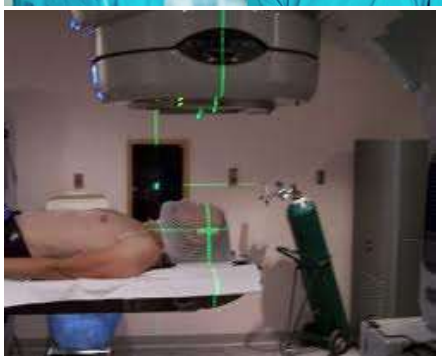
Ang et al. (2010). *New England Journal of Medicine, 363*(1), 24–35.

Recurrence



Joseph et al. Head & Neck 2016: 28 (suppl 1), E1501-9..

Treatment of early stage (stage I, II)



-one modality only
-depend on tumor localisation, patient preferences

Surgery

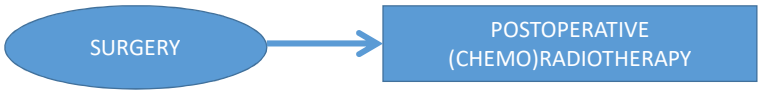
or

Radiotherapy

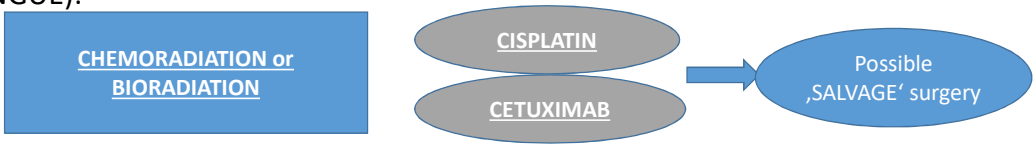
http://media-cache-ec0.pinimg.com/originals/b0/b1/11/b0b11177ebfa9dc7ae99bcce8df9bc0c.jpg

Therapy of stage III, IVa,b

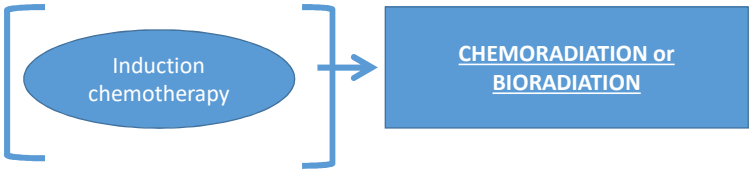
- Operable disease:



- Operable disease, but intention for organ preservation (LARINX, PHARYNX, BASE OF TOUNGUE):



- Inoperable disease:



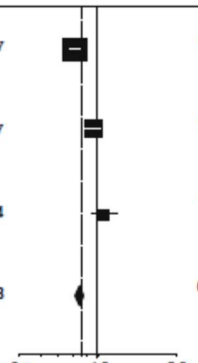
Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients

Jean-Pierre Pignon [a,*], Aurélie le Maître [a], Emilie Maillard [a], Jean Bourhis [b], on behalf of the MACH-NC Collaborative Group [1]

Radiotherapy and Oncology 92 (2009) 4–14

(a) Hazard ratio of death.

Timing	No. Deaths / No. Entered LRT+CT	LRT	O-E	Variance	Hazard Ratio	HR [95% CI]
Concomitant	3171/4824	3389/4791	-326.4	1587.7		0.81 [0.78;0.86]
Induction	1877/2740	1813/2571	-40.0	900.7		0.96 [0.90;1.02]
Adjuvant	**631/1244**	**661/1323**	**17.9**	**317.4**		**1.06 [0.95;1.18]**
Total	**5679/8808**	**5863/8685**	**-348.5**	**2805.8**		**0.88 [0.85;0.92]**



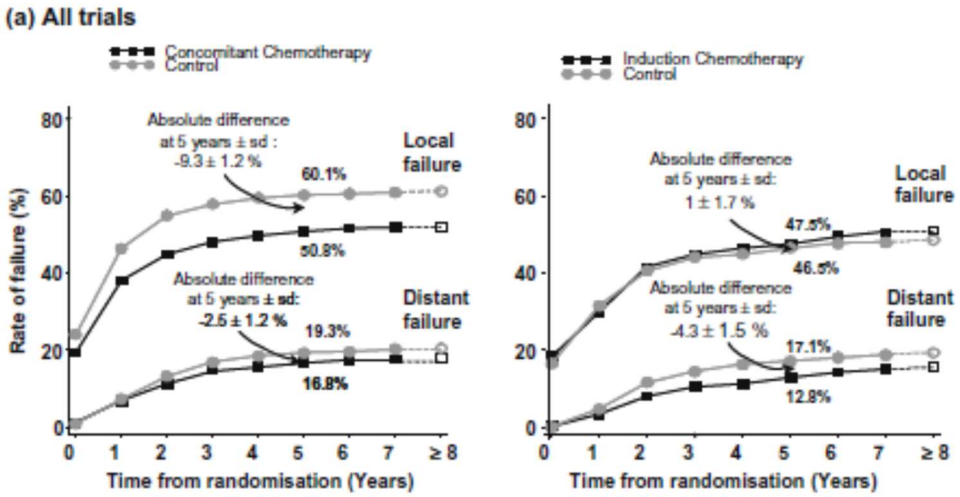
Test for heterogeneity: $\chi^2_{107} = 179.8$ $p < 0.0001$ $I^2 = 41\%$

Test for interaction: $\chi^2_2 = 26.60$ $p < 0.0001$

LRT+CT effect: p < 0.0001

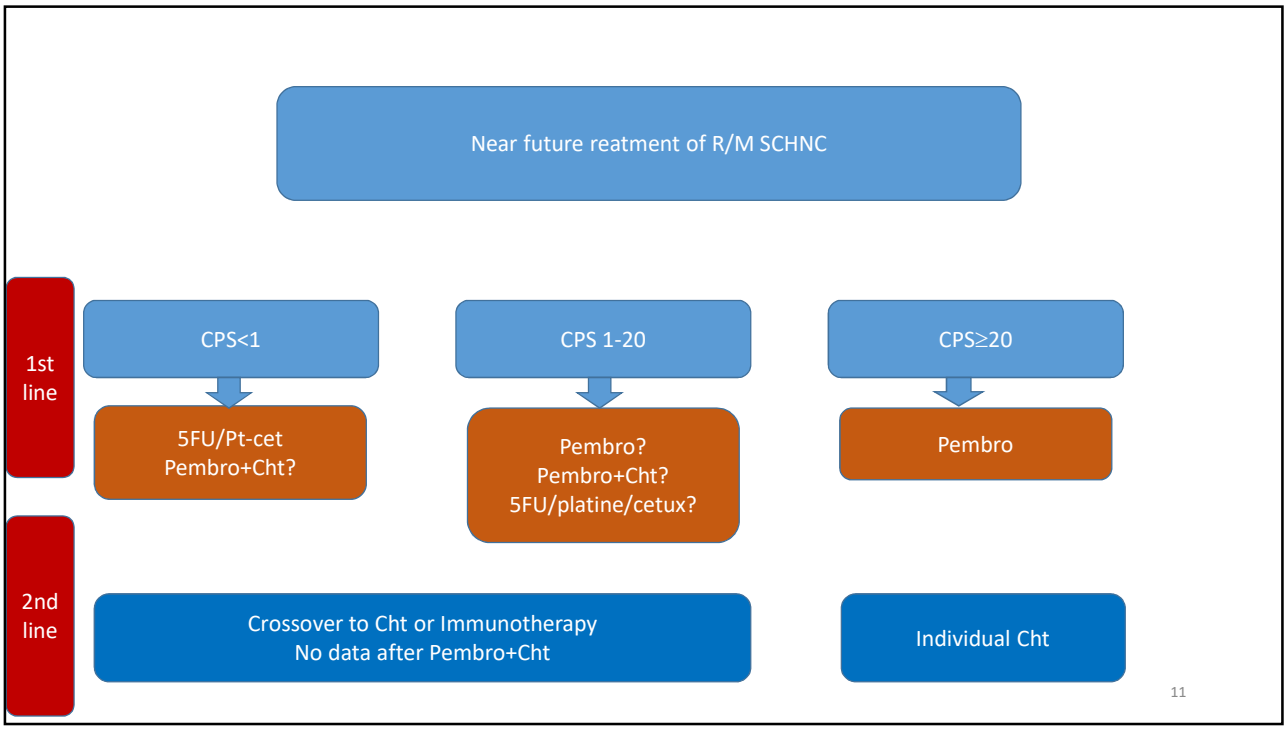
16485 pts
87 trials

Concomitant CTRT has an effect on LOCAL FAILURE and DISTANT FAILURE



Treatment of R/M SCHNC

1st line	Relapse<6 months after platine CRT → nivolumab	Reccurence>6 months after platine → 5FU/platine/cetux	Unfit for platine Cht → Individual Cht/best supportive care
2nd line	Individual Cht	Nivolumab or pembrolizumab	Nivolumab or pembrolizumab



Treatment of nasopharyngeal carcinoma: very chemo- and radiosensitive tumor

Surgery is not the option!

- Stage I: RT only
- Stage II, III, IVA:
  - Concurrent CT/RT > ACT (category 2) (ACT: 5FU/cis)
  - CT/RT (category 2a)
  - ICT > CT/RT (category 2b) (ICT: TPF, gem/cis??)
  - multimodality clinical trial

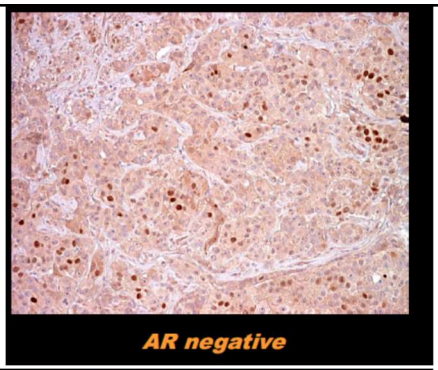
Primary metastatic or recurrent salivary carcinoma (local/regional/distant metastases)

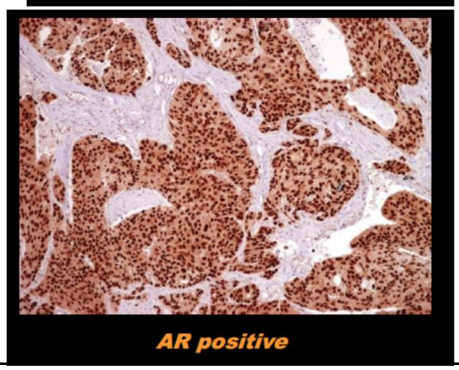
- Trial
- CT/RT
- CT > CT/RT or RT or Observation
- RT/surgery in selected pts with oligometastatic disease

- Salvage curative surgery (neck, local)
- Salvage RT (carbon or proton IMRT)
- CT (gem/cis better than 5FU/cis)
  - Other active drugs: Taxanes, IFO, FU, capecitabine, vinorelbine, gemcitabine, MTX, EDX, cetuximab (11%)
- Non active drugs: TKI
- Immunotherapy: CTL, to disrupt EBV cell latency (azacitidine..), Nivo: 20% RR, PFS at 1yr 19%

Androgen receptors in salivary gland ca. - antiandrogen therapy

- Advanced disease
- •AR high expressing cases, independently from histology (mostly SDC; AD, NOS; HG-MEC)
- •Female?
- •Which type of HT?
  - ➢ bicalutamide 50 mg/die plus LHRH agonist q4wks?
  - ➢ bicalutamide 150 mg?
- How long?





CANCER OF UNKNOWN PRIMARY SITE (CUP)

4th September 2019

Erika MATOS

Definition

- CUP is biopsy-proven malignancy for which the anatomic origin at the time of presentation remains unidentified in spite of a detailed history, physical examination and a thorough diagnostic work-up.
- CUP is a heterogeneous group of metastatic tumors, which share some common features:
  - the ability of an early dissemination,
  - clinical absence of the primary site,
  - aggressive behaviour,
  - unpredictable metastatic pattern,
  - poor response to conventional systemic cytotoxic therapy.

Abeloff's Clinical Oncology (6th Edition) 2020; Cancer of Undefined Site of Origin 1694-702.

Incidence of CUP (1)

- Rare disease?
- CUP accounts for 3-5% of all human cancers.
- CUP is considered the 8th most frequent malignant tumor.
- During the last two decades we have evidence that the incidence is decreasing (EU and USA).
- Why is it decreasing?
  - Improved diagnostics.
    - better immunohistochemistry,
    - better imaging technology and
    - molecular analyses (gene expression profiling tests and comprehensive genomic profiling)
      - which may enable us to detect the primary site more often.
  - Better smoking control.
    - Although the etiology and risk factors for CUP are poorly defined.
    - Smoking is one of the risk factors: RR 3.6 for current smokers, RR 5.1 for a heavy smokers.

Cancer medicine 2018; 7:4814-24.
Cancer Causes Control 2014; 25:747-57.

Basic diagnostic-work-up in CUP (ESMO guidelines)

- Patient's history
  - history of previous biopsies, spontaneously regressing lesions and family history
- Physical examination
  - Including rectal and breast examination.
- Good quality tissue sample (ESENTIAL!):
  - meticulous immunohistochemistry.
- Basic blood and biochemical analyses.
- CT of the chest, abdomen and pelvis.
- Mammography in women.

Diagnostic strategy should take in account the natural behaviour of the disease and the expected duration of survival based on extent of the disease and PS.
Difficult and time-consuming diagnostic studies should not compromise patients' quality of life.

Ann Oncol 2015; 26(Suppl 5): v133-138.

Additional diagnostic-work-up in CUP (1)

- Additional procedures should be sign-, symptom-, lab. abnormalities guided.
- Breast MRI: in patients with isolated axillary lymph node metastases and suspected occult primary breast carcinoma after negative mammography and sonography results.
- Broader use of MRI in CUP diagnostics is questionable.
- Endoscopy: if the patient has symptoms or relevant signs.
- FDG-PET imaging in CUP diagnostics:
  - in patients with cervical lymphadenopathy of primarily squamous histological subtype.
  - PET-CT is useful (not been prospectively studied):
    - patients presenting with solitary metastatic disease who are candidates for curative loco-regional treatment in purpose to exclude occult metastases before extensive surgery,
    - patients with known severe iodine dye allergy
    - patients with predominant bone disease who would otherwise require either multiple MRIs or bone scans to evaluate response to therapy.

Abeloff's Clinical Oncology (6th Edition) 2020; Cancer of Undefined Site of Origin 1694-702.

Additional diagnostic-work-up in CUP (2)

- Serum tumor markers have no proven prognostic, predictive or diagnostic assistance.
- Increased values of some tumor markers may help in guiding further diagnostics:
  - Beta human chorionic gonadotropin (beta-HCG) and alpha-fetoprotein (AFP):
    - in patients with midline tumor masses with undifferentiated histology.
  - Prostate Specific Antigen (PSA):
    - in men with adenocarcinoma and predominantly bone disease.

Unfortunately, most tumor markers (CEA, CA125, CA19-9 and CA15-3) are not specific and thus are not helpful in searching for the site of primary tumor.

Abeloff's Clinical Oncology (6th Edition) 2020; Cancer of Undefined Site of Origin 1694-702.

Clinical presentation of patients with CUP?

- There is no unique clinical picture.
- The majority of patients presents with symptoms and signs of metastatic disease.
- There are patients with only or manly liver metastases, with lymph node metastases in mediastinal or retroperitoneal region, with axillary lymph nodes, with cervical lymph nodes, with peritoneal disease, with malignant ascites, with lung disease only or pleural effusion only, bone only disease or metastases to CNS only, although more often as a part of disseminated disease.
- Clinical presentation depends on **number of metastatic lesions** and theirs' **distribution**.
- The majority of patients has metastatic disease in more than one organ, the most often in liver, lung, bone and lymph nodes.

Ann Oncol 2015; 26(Suppl 5): v133-138.

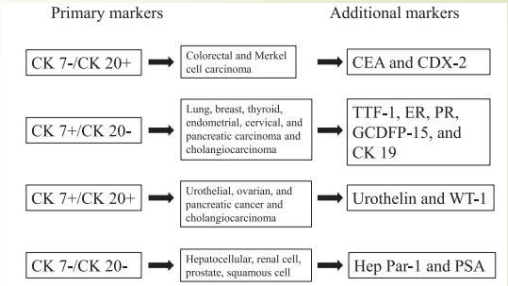
How can pathologist help? (1)

- Challenging work! Direct communication between clinician and pathologist is crucial.
- Core biopsy is preferred over fine needle aspirate specimen.
- Light microscopy: the tissue specimen (paraffin sections stained with eosine and hematoxylin)
  - Based on established cytological criteria, the pathologist usually can classify the tumors into broad groups:
    - Carcinoma (5% SSC)OR adenocarcinoma (60%),
    - Sarcoma,
    - lymphoma.
  - Some specimens will lack any cytological distinguishing features:
    - undifferentiated malignancy (35%).

Ann Oncol 2015; 26(Suppl 5): v133-138.

How can pathologist help? (2)

- IHC: significant role in the workup of CUP
  - define tumor lineage by using peroxidase-labelled antibodies against specific tumor antigens.
  - have to be directed in terms of clinical and radiological patient's data
  - random use of large numbers of tissue markers is rarely helpful
  - Staining for different CK (components of cytoskeleton of epithelial tissue) may be very helpful.
    - commonly used staining for CK7, 20, 5 and 6.
    - From the pattern of theirs' expression, the most likely site of origin can be identified. Again, the method has a limitation, no pattern is 100% specific.



The method has limitations:
- the majority of tissue markers are not specific for one organ
- no pattern is 100% specific,
- the absence of markers does not exclude the origin in certain organ/tissue.

Abeloff's Clinical Oncology (6th Edition) 2020; Cancer of Undefined Site of Origin 1694-702.

How can pathologist help? (3)

- Novel molecular studies in CUP evaluation?
- There are two main approaches:
  - Gene expression profiling tests (GEP) to identify the tissue of origin (ToO):
    - Methodology: RT-PCR evaluating the expression od different genes
    - Several assays on the market (evaluating from 10 to 92 and more genes)
  - Comprehensive genomic profiling tests (CGP) to find treatable genomic aberrations (GA):
    - methodology: NGS

Abeloff's Clinical Oncology (6th Edition) 2020; Cancer of Undefined Site of Origin 1694-702.

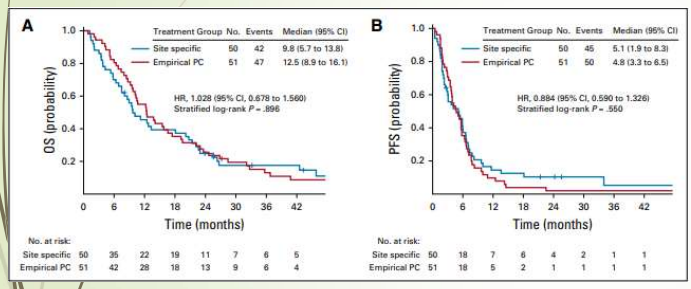
Is there a clinical benefit of identifying ToO by GEP? (1)

- GEP:
  - Has the potential to predict the origin of tumor tissue.
  - It is based on the finding that metastases have molecular signatures that may resemble to ToO.
  - The strategy has been validated in metastatic tumors with known primary site with an accuracy of 80% to 90%.

Survival of patients who received tissue-specific therapy did not differ significantly to historical cohorts, treated with empiric chemotherapy.

Abeloff's Clinical Oncology (6th Edition) 2020; Cancer of Undefined Site of Origin 1694-702.

Is there a clinical benefit of identifying ToO by GEP? (3)



Conclusion: Site-directed therapy based on microarray profiling does not improve OS or PFS compared to empirical treatment.

Hayashi H et al. JCO 2019; 37:570-9.

- ASCO 2019:
  - prospective phase II randomized study
  - 130 patients included
  - Randomization: site-specific therapy or empiric paclitaxel and carboplatin
  - GEP was used to successfully predict a tissue of origin **in all patients**.
  - **The results were disappointing.**
    - mOS: 9,8 mos for he site-specific therapy and 12,5 mos for empiric treatment (p=0,896).
    - mPFS: 5,1 mos vs 4,8 mos (p=0,55).

Current clinical role of comprehensive gene profiling (CGP) in CUP? (1)

- The trend across all cancer types is personalized medicine (CUP seem ideal candidate).
- Aim of tumor CGP (methodology is NGS): **to find aberrations that can be targeted therapeutically**:
  - FoundationOne™ assay
    - is FDA-approved for solid tumors. It is based on 324 genes. All four types of genetic aberrations can be identified (substitutions, insertion, deletion and copy number alterations, as well as MSI and TMB) using paraffin embedded tumor sample. PDL1 testing can be added.
  - MI Transcriptome™ assay.
    - provides information on 592 genes, detects gene fusions and can differentiate fusions from other rearrangements in solid tumors. The assay is supposed to get FDA approval in late 2019.

Abeloff's Clinical Oncology (6th Edition) 2020; Cancer of Undefined Site of Origin 1694-702.

Do we have effective drugs for CUP patients?

a responsive subset:

favourable prognostic subset

- about 20% of CUP patients
- should be treated with primary-specific therapy corresponding to most likely primary site

an unresponsive subset:

poor prognostic subset

- about 80% of CUP patients

Int J Cancer 2014; 135, 2475–81.
Abeloff's Clinical Oncology (6th Edition) 2020; Cancer of Undefined Site of Origin 1694-702.

Favourable prognostic subset

- Traditionally defined favourable subset:
  - women with isolated axillary adenopathy,
  - women with serous papillary peritoneal carcinomatosis,
  - squamous cell carcinoma involving mid-high cervical lymph nodes,
  - poorly as well as well-differentiated neuroendocrine carcinoma,
  - poorly differentiated and undifferentiated carcinoma (extra gonadal germ cell cancers),
  - men with blastic bone metastases and elevated PSA
  - patients with single, small and potentially resectable tumors
- Newly identified favourable CUP subset:
  - patients who look like CRC (CK 20 pos, CK 7 neg, CDX pos), should be treated as patients with advanced CRC (expected RR around 50% and mOS up to 3 years)

Abeloff's Clinical Oncology (6th Edition) 2020; Cancer of Undefined Site of Origin 1694-702.

Unfavourable prognostic subset (1)

- Sensitivity to chemotherapy is modest.
- GEP could identify ToO in majority of these patients.
  - If identified tissue specific therapy or inclusion into clinical trial (if available) is the best option.
  - If not-identified, the option is either clinical trial or CGP in terms to identify potentially treatable GA
    - in many countries expensive molecular assays are not available or not covered by insurance
    - targeted drugs and check point inhibitors are not covered by insurance
    - **at the time being we have no prove that such approach really influence patients' survival.** Data from well designed clinical trials are necessary.

Unfavourable prognostic subset (2)

- The majority of patients from this subset have poor prognosis.
- At presentation, two-thirds of patients have metastatic lesions in two or more visceral sites (most often liver, lung, lymph nodes and/or peritoneum).
- Patients are often in poor performance status.
  - For many of these patients BSC is the best option.
  - For selected patients empiric chemotherapy is justified.
  - Cisplatin or taxane-based doublets have been used, with little impact on survival.
  - Patients and relatives have to be informed that expected RR to ChT is only 20% to 30% and expected mOS not more than 9 to 11 mos. This might influence theirs' decision about treatment.

NCCN guidelines

Conclusions

- CUP is a heterogeneous disease with poor prognosis.
- It is mandatory to establish to which prognostic group the patient belongs to.
- In patients belonging to a favourable prognostic subset long-term survival can be achieved with appropriate treatment.
- Patients classified to unfavourable prognostic subset have to be informed about benefits and disadvantages of empiric therapy. Especially for patients with widespread disease and poor PS BSC is the best option.
- Novel approaches are promising, present a fundamental shift in the paradigm of treatment of cancer patients from tissue-specific to individual, patient customized treatment, directed according to tumor specific GAs.

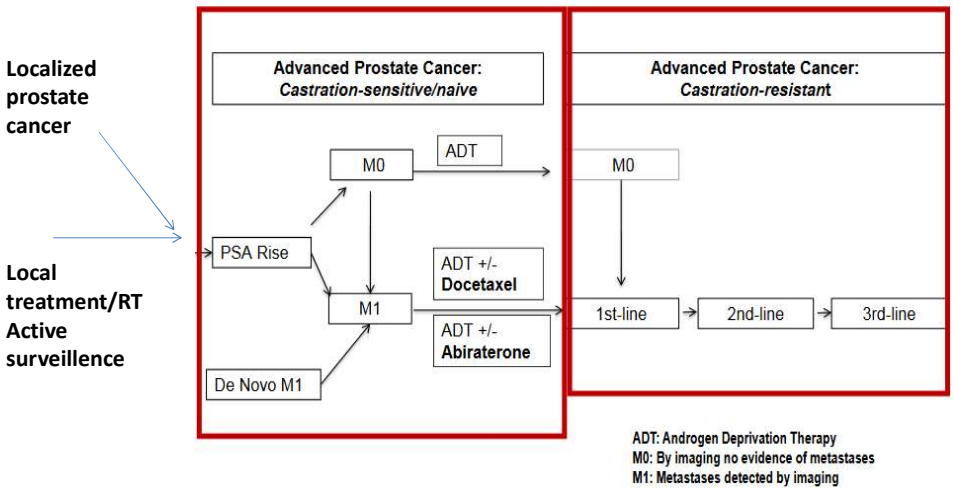
Systemic treatment of prostate cancer

Borislav Belev

Clinical Hospital Center Zagreb
School of Medicine Zagreb

1st Summer School in medical oncology –Ljubljana, 3.-6. September 2019

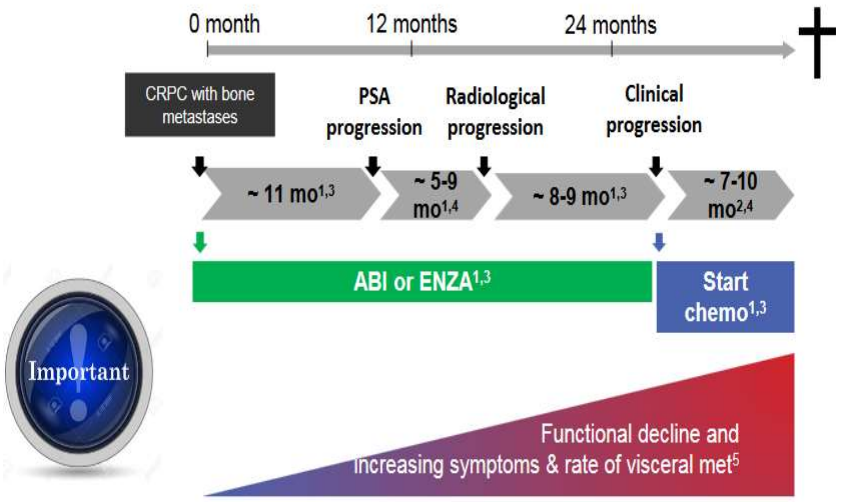
Prostate cancer – possible scenarios



Approved therapies for CRPC

ADT=androgen-deprivation therapy; mCRPC=metastatic castration-resistant prostate cancer.

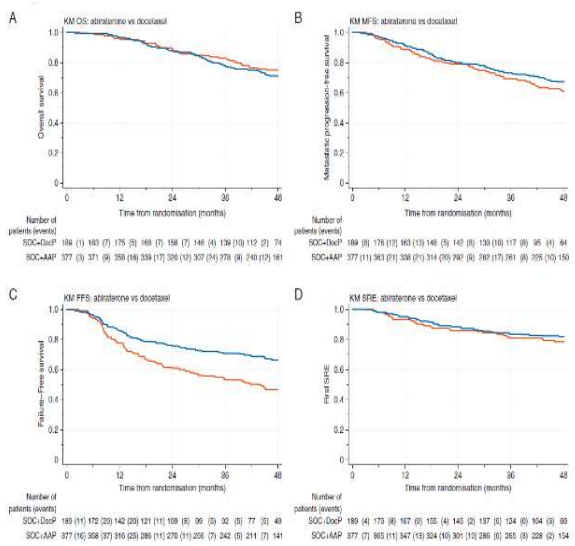
Time to events in the COU-AA-302 and PREVAIL studies

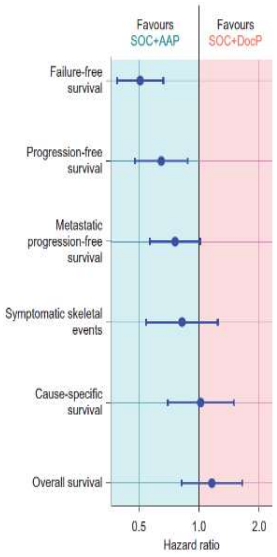


1. Ryan CJ et al. N Engl J Med 2013;368:138-48; 2. Ryan CJ et al. Lancet Oncol 2015;16:152-60; 3. Beer TM et al. N Engl J Med 2014;371:424-33; 4. Beer TM et al. Eur Urol 2017;71:151-4; 5. Pezaro CJ et al. Eur Urol 2014;65:270-3

Abiraterone or Docetaxel?

Directly randomised data from the STAMPEDE: 566 pts





Sydes et al. Annals of Oncology 29: 1235–1248, 2018

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 28, 2018 VOL. 378 NO. 26

Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer

Maha Hussain, M.D., Karim Fizazi, M.D., Ph.D., Fred Saad, M.D., Per Rathenborg, M.D., Neal Shore, M.D., Ubirajara Ferreira, M.D., Ph.D., Petro Ivashchenko, M.D., Eren Demirhan, Ph.D., Katharina Modelska, M.D., Ph.D., De Phung, B.S., Andrew Krivoshik, M.D., Ph.D., and Cora N. Sternberg, M.D.

ORIGINAL ARTICLE

Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer

Matthew R. Smith, M.D., Ph.D., Fred Saad, M.D., Simon Chowdhury, M.B., B.S., Ph.D., Stéphane Oudard, M.D., Ph.D., Boris A. Hadaschik, M.D., Julie N. Graff, M.D., David Olmos, M.D., Ph.D., Paul N. Mainwaring, M.B., B.S., M.D., Ji Youl Lee, M.D., Hiroji Uemura, M.D., Ph.D., Angela Lopez-Gitlitz, M.D., Géralyn C. Trudel, Ph.D., Byron M. Espina, B.S., Youyi Shu, Ph.D., Youn C. Park, Ph.D., Wayne R. Rackoff, M.D., Margaret K. Yu, M.D., and Eric J. Small, M.D., for the SPARTAN Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer

Karim Fizazi, M.D., Neal Shore, M.D., Teuvo L. Tammela, M.D., Ph.D., Albertas Ulys, M.D., Egils Vjaters, M.D., Sergey Polyakov, M.D., Mindaugas Jievaltas, M.D., Murilo Luz, M.D., Boris Alekseev, M.D., Iris Kuss, M.D., Christian Kappeler, Ph.D., Amir Snapir, M.D., Ph.D., Toni Sarapohja, M.Sc., and Matthew R. Smith, M.D., Ph.D., for the ARAMIS Investigators*

Take home messages

- Optimal sequence of treatment is not defined, since prostate cancer is heterogenous disease
- Treatment paradigm is changing dynamicaly, there are many new agents evolving in the last decade
- Androgen deprivation therapy is still fundamental
- Understanding of pathophysiology of disease determined new strategies, recognizing AR-pathway as still very important even in castrate situation
- Focus of treatment strategy is shifted toward earlier phases of disease, providing more benefitial outcomes
- Enzalutamide produces good therapy effect in mCRPC, abiraterone-acetat in mCRPC and mCSPC
- Docetaxel is valid option in mPC
- Cabazitaxel, mitoxantron and carboplatine are the options in mCRPC
- Apalutamide and enzalutamide are good option in m0CRPC
- New area of diagnostics – tumor genetic analysis – provides more individua-tailored treatment approach

Univerza v Ljubljani

Advances in treatment of renal cell carcinoma

Onkološki inštitut Ljubljana

Bostjan Seruga, MD, PhD

Division of Medical Oncology

Institute of Oncology Ljubljana and University in Ljubljana

Ljubljana, September 4, 2019

Topics

- Role of surgery in advanced RCC
- Targeted Therapy for Advanced RCC
- Immune Checkpoint Inhibitors for Advanced RCC
- Combination Therapy: Current and Future Opportunities
- Optimal Sequencing of Systemic Therapy in Advanced RCC
- Nuances in Treating Patients: Adjuvant Therapy, Treating Brain Metastases, Managing Adverse Events

Take-home Messages 1

- **The key for cytoreductive nephrectomy is patient selection**
  - **Cytoreductive nephrectomy should no longer be considered standard of care in intermediate- and poor-risk groups of metastatic RCC at least when medical treatment is required**
- **Radical metastasectomy followed by observation is commonly used strategy in selected patients with oligometastatic disease. There is no role of trageted agents in patients who underwent radical metastasectomy**

Take-home Messages 2

- **Small molecule targeted agents dramatically improved the outcome of patients with metastatic RCC**
- **Sequencing of small targeted agents should be based on the currently available evidence**
- **In the era of checkpoint inhibitors small molecule targeted agents remain important therapeutic strategy for patients with metastatic RCC**

Take-home Messages 3

- Anti–PD-1 based therapy is active in treatment-naive patients including favorable-risk patients
- Much, but not all, of the activity of nivo/ipi is likely from the anti–PD-1 component
- Anti–PD-1 monotherapy with nivo/ipi salvage might be a reasonable strategy when one is concerned about the toxicity of nivo/ipi
- A trial of nivo/ipi vs nivo in frontline RCC is indicated

Take-home Messages 4

- Most immune-related AEs are reversible with immunosuppression through steroid treatment
  - Typically start with high-dose IV and then taper over 1-3 mos
  - Exception: adrenal insufficiency and hypothyroid need replacement hydrocortisone and levothyroxine, respectively, without use of steroids
- No evidence that intervening with steroids curtails antitumor efficacy of agent

Take-home Messages 5

- **Adjuvant VEGF therapy, when adequately dosed, can offer very modest benefit balanced against toxicity**
- **The goal of a patient with newly metastatic RCC is potential cure; therefore, regimens with the highest chance of cure/durable response, balanced against acceptable toxicity/time off of treatment, should be prioritized**
- **Immunotherapy-based regimens offer the best chance of achieving patient goals**
  - **Whether immunotherapies in combination with one another or with VEGF therapies most effectively achieves these goals is as yet undefined**

IO–Non-IO Combinations

- **IO is different than tumor-directed therapy because of its ability to produce Treatment-Free Survival (TFS)**
- **Combinations that improve median PFS or median OS without producing TFS may sacrifice the potential of IO while contributing toxicity, inconvenience, and tremendous extra cost**
- **Not only must A+B > A followed by B (or B followed by A), but TFS must be maintained in order for such combos to be fully embraced**
- **Clinical trials with IO agents need to use IO endpoints**

ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY
LJUBLJANA

Naslov

Systemic treatment of bladder cancer

Marina Mencinger MD , PhD

International School for Medical Oncology
Ljubljana Sept 2019

Tumours of the urothelial tract

Cancer that starts in the urothelium is called urothelial (or transitional cell) cancer. By definition, urothelial carcinoma with divergent differentiation refers to tumours arising within the urothelial tract, in which some percentage of “usual type” urothelial carcinoma is present along with other morphologies

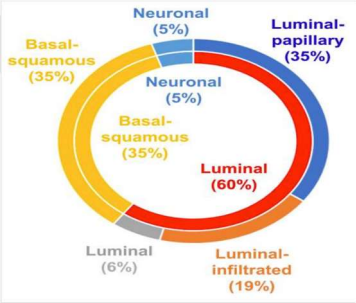
Histological type (1)	
Urothelial carcinoma	90-95%
Squamous-cell carcinoma	3%
Adenocarcinoma	2%
Small-cell carcinoma	<1%

Bladder Cancer (2)		
Superficial	pTa, pTis, pT1	75-85%
Muscle-invasive	pT2, pT3, pT4	10-15%
Metastatic	N+, M+	5%

1. Humphrey, European Urology 2016,
2. Matulay J, F1000Res. 2018;

Molecular characterisation of bladder c.

The TCGA (The Cancer Genome Atlas) study confirmed the existence of luminal (KRT20+, GATA3+, FOXA1+) and basal (KRT5,6,14+, GATA3−, FOXA1−) transcriptional sub- types, and neuronal subtypes-1.
The subtypes were associated with overall survival (retrospectively)-2.
Luminal-best OS, basal-most improvement in OS with NAC, claudine low-poor OS.



Using a novel single-patient subtype classifier based on The Cancer Genome Atlas identified 11 patients with a neuronal subtype, with 72% response rate to atezolizumab.-3

Rodriguez V Cancer Treat Res 2018; Seiler, Eur Urology 2017; Kim, Europ Urol., 2019

Muscular invasive bladder carcinoma has bad prognosis in comparison to muscular noninvasive

clasification	Stadium at diagnosis	Percentage of patients		5 year OS[1]	RIsk for relaps in 5 years
Muscular noninvasive	noninvasive (Ta, Tis ,T1)	51–75%[1–4]		96%	50–90%[2,4]
Muscular invasive	Localised (T2–4, N0)	35%[1]	30%[4]	69%	≈50%[6]
	Localy advanced (Tx, N1)	7%[1]		34%	
metastatic	(Tx, Nx, M1)	4%[1,5]		6%	NA

ISSUES!

1. Howlader N, et al. (eds). SEER Cancer Statistics Review, 1975–2011. **2.** NCCN Guidelines – Bladder cancer v1.2015. **3.** Sharma S, et al. Am Fam Physician 2009. **4.** Kaufman DS, et al. Lancet 2009. **5.** American Cancer Society 2014: Bladder Cancer. **6.** de Vos FY and de Wit R. Ther Adv Med Oncol 2010.

RATIONALE FOR NAC–prolonged OS: T2-4a, No, Mo: Neoadjuvant CT with platinum

Trial	n	Neoadj. CT + surgery vs. surgery alone
Meta-analysis 11 trials[1]	3.005	Statistically significant prolonged OS (HR=0,86; 95% CI: 0,77–0,95; p=0.003) • 5% absolute improvment 5 – y OS (from 45% na 50%)[2] Statistically significant prolonged survival without disease (HR=0,78; 95% CI: 0,71–0,86; p<0,0001) • 9% absolute improvement in 5 – y survival without disease

Recommended CT schemes by NCCN-2
3-4 cycles dd-MVAC : dose-dense metotreksat, vinblastin, doksorubicin in cisplatin)
4 cycles gemcitabin in cisplatin
3 cycles **CMV** (cisplatin, metotreksat, vinblastin)

1- Advanced Bladder Cancer Meta-analysis Eur Urol 2005 2-National Comprehensive Cancer Network. Bladder Cancer (Version 1.2019).

Rationale ACT: T3/4, N+, Mx: adjuvant CT

trial	n	Surgery + adjuv. CT vs surgery alone
Meta-analysis of 9 trials (1)	945	Statistically significant prolongation of OS (HR=0,77; 95% CI: 0,59–0,99; p=0,049) Statistically significant prolongation of survival withouth disease (HR=0,66;
EORTC (2)	284	PFS was longer with immediate versus deferred adjuvant chemotherapy [Hazard ratio (HR): 0.54; $p < 0.001$], but no diferences in OS were observed (HR 0.78; $p = 0.13$)

Randomised trials of adjuvant therapy are incomplete or underpowered.

1-Leow JJ, Eur Urol 2014; 2-Sternberg, Lancet Oncol 2015

Bladder sparing treatments : T2, No, Mo

Who are optimal candidates for bladder preservation?

Optimal candidates for bladder preservation with chemoradiotherapy include patients with tumors that present without hydronephrosis, are without concurrent extensive or multifocal Tis, and are <6 cm. Ideally, tumors should allow a visually complete or maximally debulking TURBT. See Principles of Radiation

1. TURBT + Concurrent chemoradiotherapy
2. Radiotherapy
3. TURB plus BCG

→ Reasses tumor status after 2-3 m

↓ Tumor present

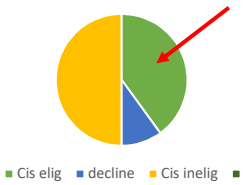
- CT
- CT+RT
- Paliative TURBT/salvage cystectomi
- BSC

Morales R, Clin Transl Oncol. 2011; NCCN guidelines 2019

1. Line treatment-cisplatin fit

The standard of care for first-line (1L) metastatic urothelial carcinoma (mUC) is cisplatin-based combination chemotherapy (NCCN V2.2019).

Eligibility for Cis NAC



Not eligible for cisplatin

ECOG PS 2	Baseline CrCl <60 mL/min	Hearing Loss Grade ≥2	Heart Failure Class III	Peripheral Neuropathy Grade ≥2

, NCCN guidelines, 2019 Galsky MD, et al. J Clin Oncol. 2011;

How do different cisplatin regimens compare (met or advanced bladder ca.)?

	GemCis	M-VAC	DD-MVAC	MVAC	DD Gem-Cis	DD M-VAC
mOS	=		=		=	
toxicity	<		<		<	
Quality of life	=		?		?	

ITT (263)	DD MVAC (6x)	MVAC (4x)	P-vrednost
5 y OS	21,8%,	13,5%	0,042
(RR)	72%	58%	0,016
Febrile neutropenia	10%	26%	0,001
(CR)	25%	11%	0,006

More ORR and CR.

von der Maase et al, J Clin Oncol, 2000; Sternberg et al, J Clin Oncol, 2001; Bamias, Ann Oncol., 2013, Sternberg et al, 2006, Eur J Can

1. Line (cisplatin ineligible or CT naïve in met setting))-NO randomised data!

		No	ORR all	DCR	ORR PD-L1 pos.	ORR in PD-L1 neg	mOS	Adverse events gr 3-4
Phase II, nonrandom, cohort 1 IMVIGOR 210	atezo	119	24% (CR 10%)		28% (CR 13%)	21 % (CR 8%)	16,3 m	18%
Phase II, nonrand Keynote 52	pembro	370	29% (CR 7%)	47%	51%	23%	11,5 m	16%

Eligibility for Cis NAC

1/3 to ½ pts are PD-L1 positiive

Balar , Lancet 2017. Vuky J, et al. ASCO 2018. Abstract 4524.; Balar AV, et al. ASCO 2018. Abstract 4523.

Why do we need PDL-1 positivity for first line?

EMA restricts use of Keytruda and Tecentriq in bladder cancer

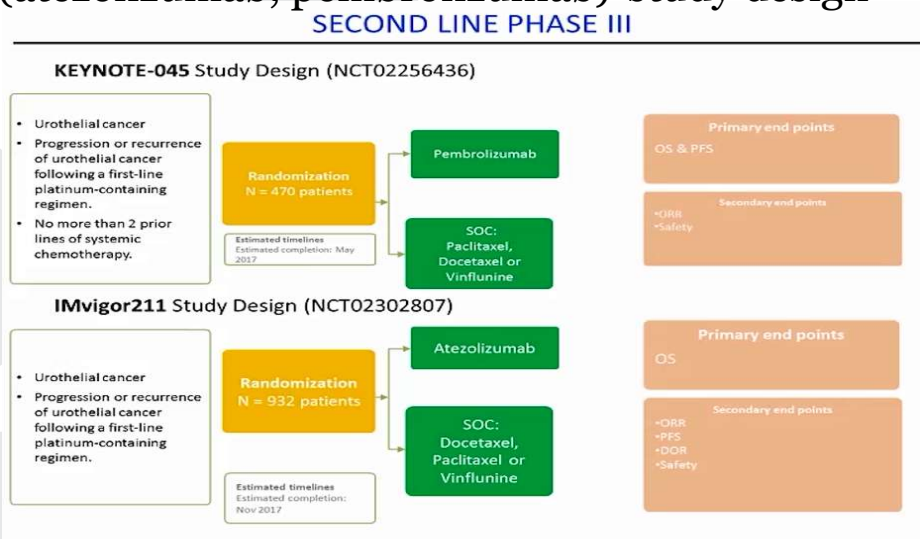
Data show lower survival in some patients with low levels of cancer protein PD-L1

Based on unreviewed data from rand. phase III trials. The results are not published yet.

PEMBROLIZUMAB:
Clone: 22C3
Combined positive score ≥10
the ratio of PD-L1–expressing **tumor-infiltrating immune cells relative to the total number of tumor cells**

ATEZOLIZUMAB:
Clone: SP142
staining on **tumor-infiltrating immune cells** covering at least **≥ 5%**

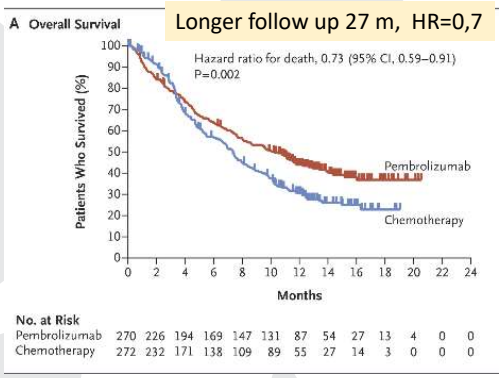
Second line phase III trials with PDL-1 inhibitors (atezolizumab, pembrolizumab)-study design



Bellmunt 2017, NEJM, Powels Lancet 2018

2.Line: Pembrolizumab vs CT: mOS and duration of response

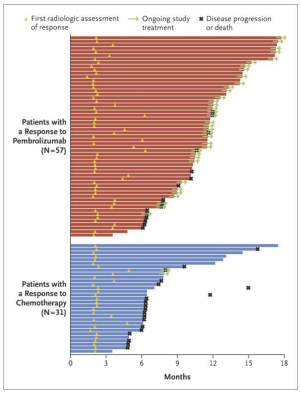
mOS



Longer follow up 27 m, HR=0,7

Duration of response

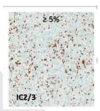
Response duration[2,3]		
Median in months (range)	Not reached (1.6+, 15.6+)	4.3 (1.4+, 15.4+)
Number (%[a]) of patients with duration ≥6 months	41 (78%)	7 (40%)
Number (%[a]) of patients with duration ≥12 months	14 (68%)	3 (35%)



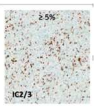
Time to Response and Duration of Response in Patients with a Confirmed Objective Response.

Bellmunt, NEJM, 2017

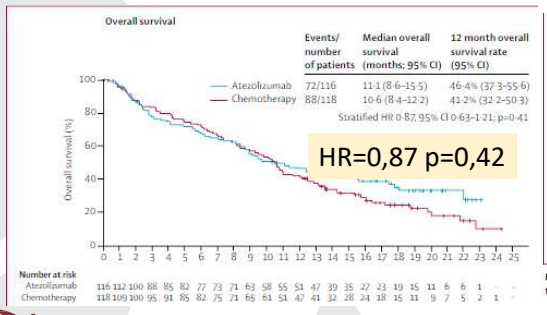
2. Line : Atezolizumab vs CT PDL1 positive patient group



mOS



Duration of response



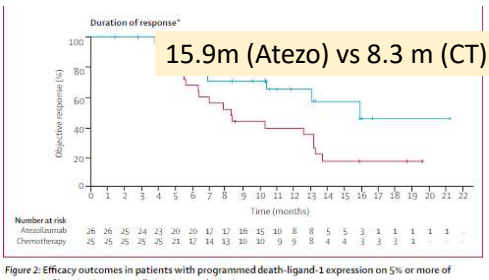
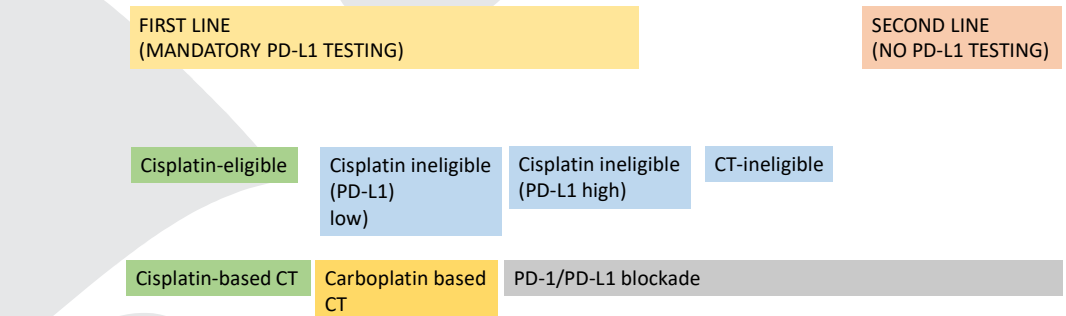


Figure 2: Efficacy outcomes in patients with programmed death-ligand-1 expression on 5% or more of tumour-infiltrating immune cells (IC2/3 population)

Powles, Lancet, 2018

Summary of Treatment in bladder cancer



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PALLIATIVE CARE
When to start and how to lead

Maja Ebert Moltara, MD
mebert@onko-i.si
Head of a Department for Acute Palliative Care
Department of Medical Oncology

ESMO Designated Centers of Integrated Oncology and Palliative Care

3-6 September 2019, Ljubljana, Slovenia

6 BASIC QUESTIONS:

WHAT?

For WHO?

WHO provides?

WHERE?

WHEN?

WHY?

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WHAT?

WHO definition of palliative care

Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.

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COMPREHENSIVE PALLIATIVE CARE

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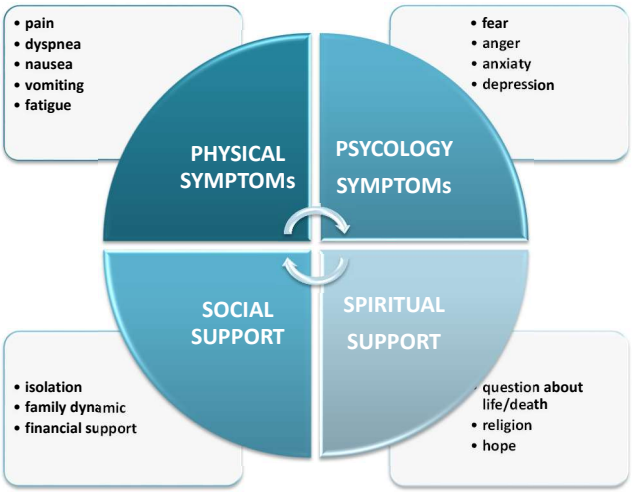
COMPREHENSIVE PALLIATIVE CARE



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WHO provides and WHERE?

All medical and non-medical members of teams in institutions where incurable patients are treated.

Basic palliative care (80% patient):
All levels of health system
(hospitals, community health centre, at home, senior homes, hospicih...)
All.

Specialied palliative care (20%):
Does not substitute basic palliative care, but it upgrade it for the patients with the most difficult and complex problems
Specialized teams (acute palliative care departent, mobile PC team)

EAPC: White Paper on standards and norms for hospice and palliative care in Europe

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CONTINOUS PALLIATIVE CARE

SENIOR HOMES

REGIONAL HOSPITALS

PATIENT WITH A FAMILY

FAMILY DOCTOR AND DISTRIC NURSE

EMERGANCY TEAM

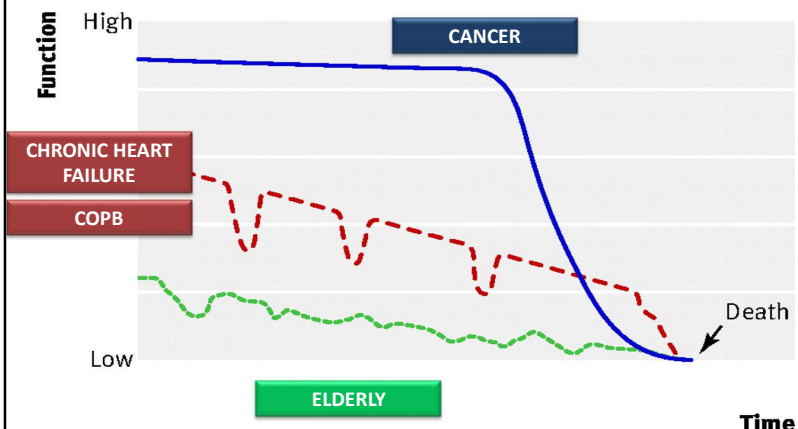
PC MOBILE TEAM

UNIVERSITY HOSPITALS

HOSPIC MOVEMENT

Hospic

For WHO?



Murray, S. A et al. BMJ 2008;336:958-959

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WHEN?

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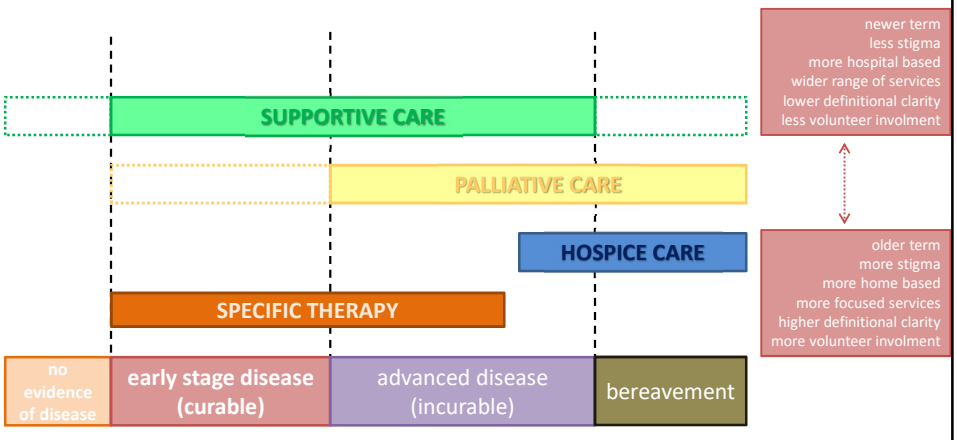
Conceptual framework



Hui, D. *et al.* Concepts and definitions for "supportive care," "best supportive care, " "palliative care, " and "hospice care" in the published literature, dictionaries, and textbooks. *Support. Care Cancer* 21, 659–685 (2013).

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WHEN?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early Palliative Care for Patients with Metastatic Non–Small-Cell Lung Cancer

Jennifer S. Temel, M.D., Joseph A. Greer, Ph.D., Alona Muzikansky, M.A., Emily R. Gallagher, R.N., Sonal Admane, M.B., B.S., M.P.H., Vicki A. Jackson, M.D., M.P.H., Constance M. Dahlin, A.P.N., Craig D. Blinderman, M.D., Juliet Jacobsen, M.D., William F. Pirl, M.D., M.P.H., J. Andrew Billings, M.D., and Thomas J. Lynch, M.D.

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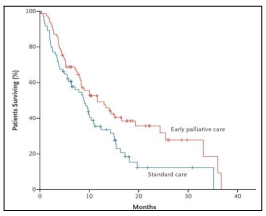
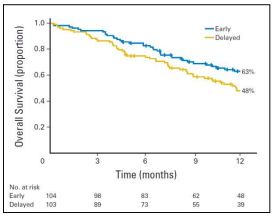
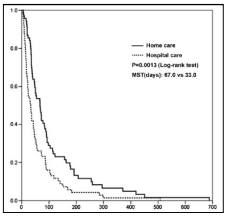
EARLY PALLIATIVE CARE



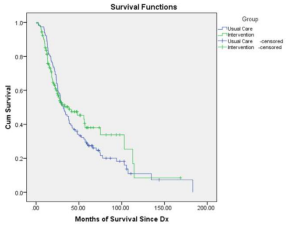
Temel, NEJM 2010



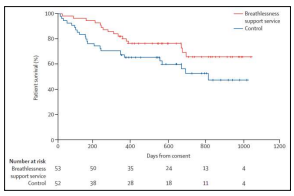
Bakitas, JCO 2015



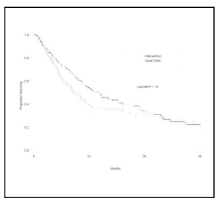
Murakami BMC Pall 2015



Ferell, J Pain Manag, 2015



Higginson 2015



Bakitas, JCO 2013

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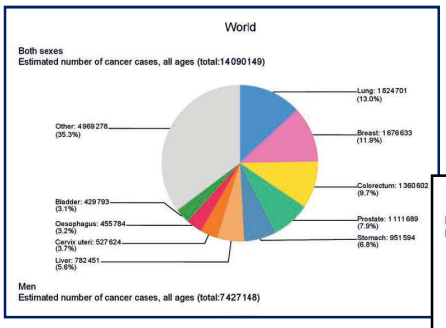
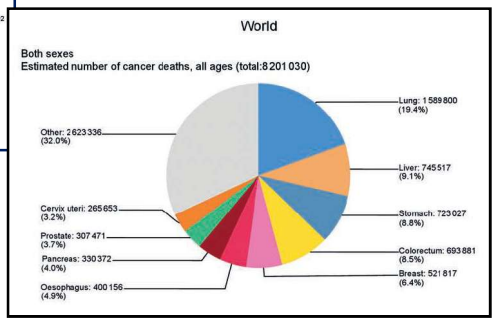
Extra: HOW many?





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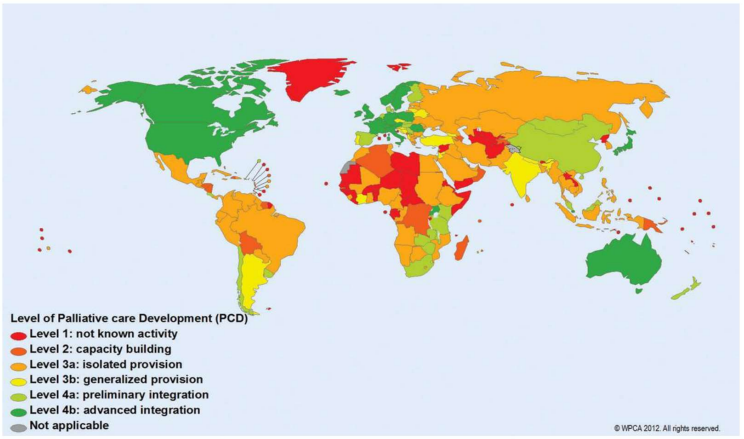
Global Atlas of Palliative Care at the End of Life, January 2014

Figure 1 World Map of Palliative Care Development 2011



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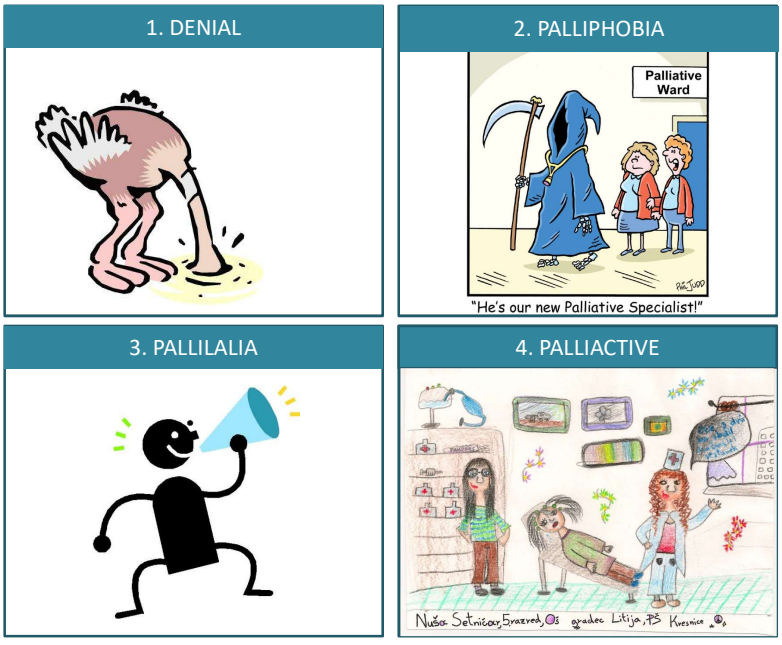

Top 10 Things Palliative Care Clinicians Wished Everyone Knew About Palliative Care

Jacob J. Strand, MD; Mihir M. Kamdar, MD; and Elise C. Carey, MD

2013 Mayo Foundation for Medical education an Research, Mayo Clin Proc. 2013; 88 (8):859865

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Onkološki Inštitut Institute of Oncology Ljubljana 80 let years

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SEKCIJA ZA INTERNISTIČNO ONKOLOGIJO

Slovensko Zdravniško Društvo

#1. SUMMER SCHOOL IN MEDICAL ONCOLOGY

Part 2 – Thursday (5.9.) & Friday (6.9.)

LJUBLJANA
3-6. SEPTEMBER 2019

Strokovni odbor:
izr. prof. dr. Janja Ocvirk, dr.med.
doc. dr. Martina Reberšek, dr.med.
dr. Simona Borštnar, dr.med.
doc. dr. Cvetka Grašič, dr.med.
dr. Tanja Mesti, dr.med.
Marko Boc, dr.med.

Organizacijski odbor:
izr. prof. dr. Janja Ocvirk, dr.med.
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dr. Tanja Mesti, dr.med.
Marko Boc, dr.med.
ga. Lidija Kristan

Uredniki zbornika:
Marko Boc, dr.med.
doc. dr. Martina Reberšek, dr.med.
izr. prof. dr. Janja Ocvirk, dr.med.
dr. Tanja Mesti, dr.med.

Organizator in izdajatelj (založnik):
Onkološki inštitut Ljubljana
Sekcija za internistično onkologijo
Katedra za onkologijo

Ljubljana, september 2019

AGENDA & INDEX

Thursday, September 5

Part 1	***Moderator: dr. Borštnar***	
8:30-10:00	*Early and locally advanced Breast cancer*	
	(dr. Borštnar, dr. Ribnikar, dr. Bešlija)	
	Introduction (20-30 min) (Dr. Borštnar)	
	Case 1: HR+HER2- luminal A BC (dr. Geršak, dr. Borštnar)	
	Case 2: HR+HER2- luminal B BC (dr. Prepeluh, dr. Borštnar)	
	Case 3: Early TNBC (dr. Geršak, dr. Borštnar)	
	Case 4: First-line ribociclib in primary metastatic hormone receptor-positive breast cancer (dr. Rugelj, dr. Borštnar)	
10:00-10:15	Break	
10:15-11:45	*Metastatic breast cancer*	
	(dr. Borštnar, dr. Ribnikar, dr. Bešlija)	
	Introduction (20-30 min) (Dr. Ribnikar)	
	Case 5: Metastatic HR+ BC with visceral crisis (dr. Dobovišek, dr. Borštnar)	
	Case 6: Primary metastatic HER2+, HR+ BC (dr. Dobovišek, dr. Borštnar)	
	Case 7: Metastatic TNBC (dr. Dobovišek, dr. Borštnar)	
11:45-12:00	Discussion	
12:00-12:30	Systemic treatment of sarcomas (dr. Unk)	
12:30-13:20	Lunch break	
Part 2	**Moderators: dr. Kandolf Sekulović, dr. Ocvirk**	
13:20-14:00	Satellite symposium (MSD)	
14:00-14:30	Adjuvant treatment strategies for malignant melanoma (dr. Herceg)	
14:30-15:15	Melanoma 2020 Standards of care and unmet needs (dr. Kandolf Sekulović)	
15:15-15:30	Discussion	
15:30-15:40	Break	
15:40-16:10	Systemic treatment of non melanoma skin cancers (dr. Ocvirk)	
16:10-17:10	Interesting cases from audience Case 1: Skin toxicity of immunotherapy (dr. Vermiglio, dr. Mesti)	
17:10-17:40	Satellite symposium	

Friday, September 6

	Moderators: dr. Reberšek, dr. Ebert Moltara	
8:30-9:30	Interesting cases from audience	
9:30-10:00	Systemic treatment of ovarian cancer (dr. Škof)	
10:00-11:00	How to manage patients with renal insufficiency (dr. Milanez)	
11:00-11:30	Side effects of immunotherapy and the management	
	(dr. Hribernik, dr. Reberšek)	
11:30-11:40	Break	
11:40-12:30	Side effects of chemotherapy (including extravasation) and TKI and the management (dr. Ovčariček, dr. Bokal)	
12:30-13:00	Discussion and conclusions	

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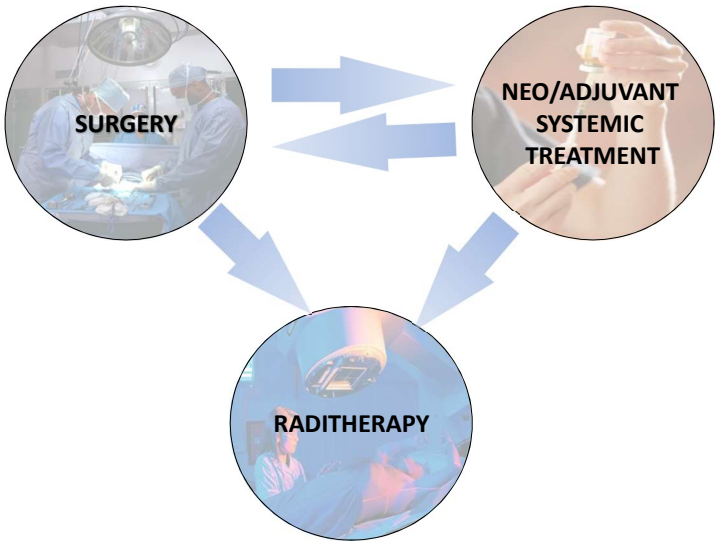
Treatment of early and locally advanced breast cancer

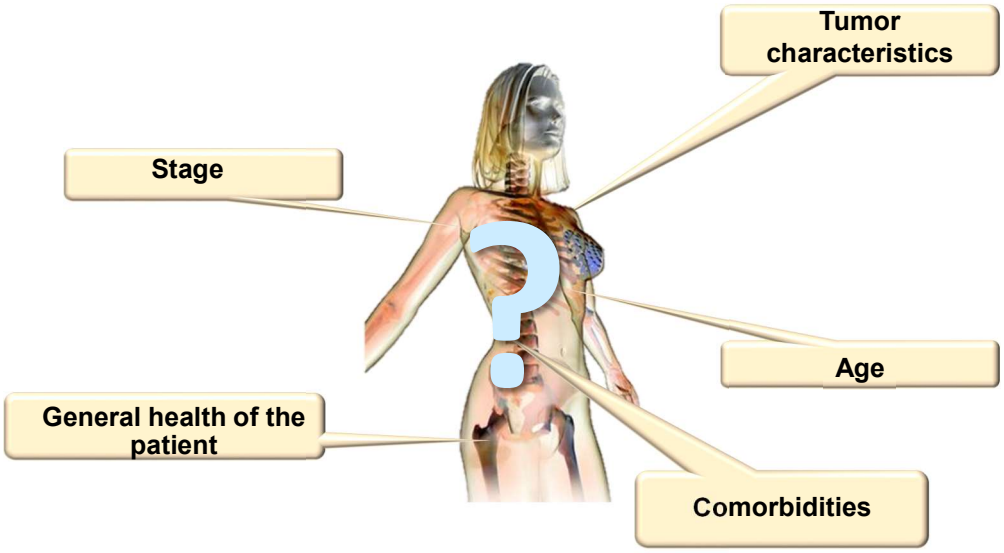
Simona Borštnar

1st Summer School of Medical oncology,
September 2019, Ljubljana

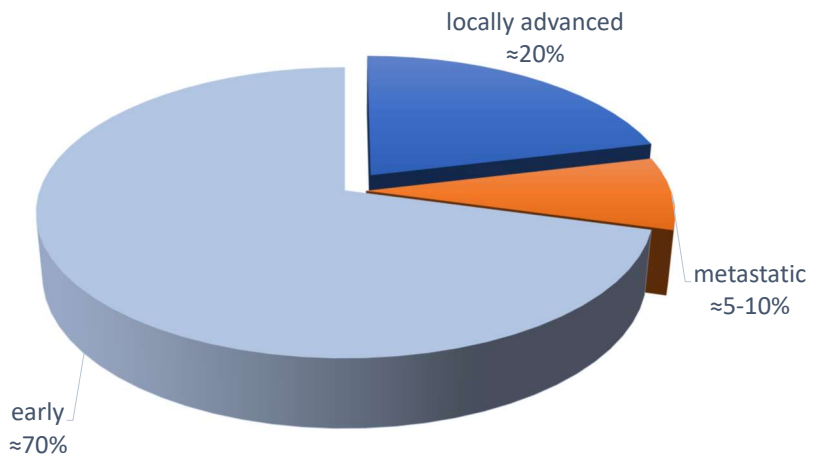
Multidisciplinary approach in treatment of breast cancer



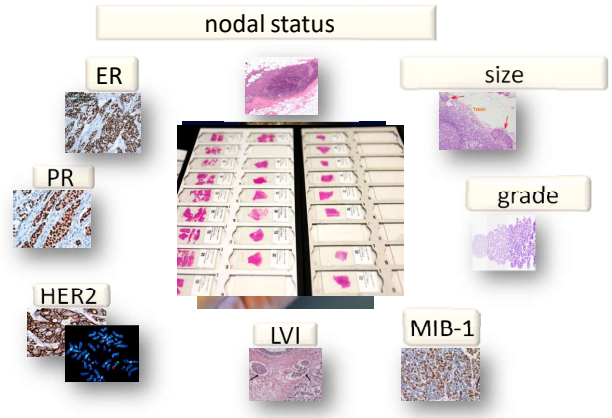
Features for selection of treatment



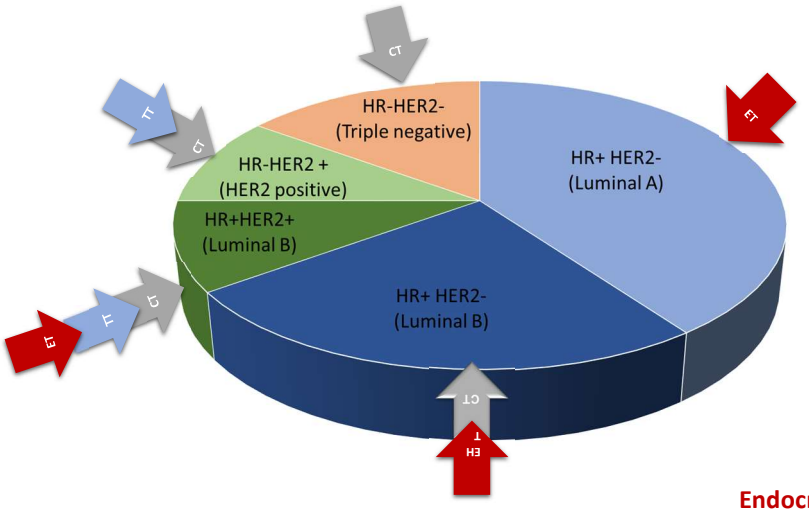
Distribution of patients by stage



Tumor characteristics



Division into subtypes and treatment decision

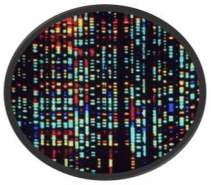


Endocrine therapy (ET)

Chemotherapy (CT)

anti HER2 therapy (TT)

Gene signatures in ER+ subtype



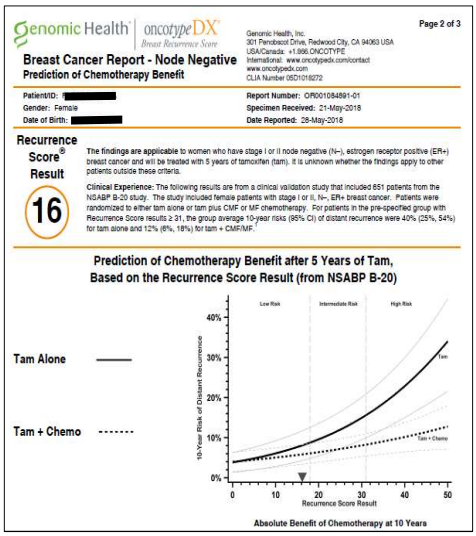
HUMAN GENOM:
~25 000 genes

GENES RELATED TO PROLIFERATION AND INVASION OF BREAST CANCER:
231 genes

- MammaPrint (70 genes)
- Oncotype (21 genes)

The 70-gene and the 21-gene signatures identify patients who may not require adjuvant chemotherapy.

Oncotype DX



Genomic Health | oncotypeDX Breast Recurrence Score

Page 2 of 3

Genomic Health, Inc.
301 Penobscot Drive, Redwood City, CA 94063 USA
USA/Canada: +1.866.ONCOTYPE
International: www.oncotypedx.com/contact
www.oncotypedx.com
CLIA Number 05D1016272

Breast Cancer Report - Node Negative
Prediction of Chemotherapy Benefit

PatientID: [redacted]
Gender: Female
Date of Birth: [redacted]

Report Number: OR001084891-01
Specimen Received: 21-May-2018
Date Reported: 28-May-2018

Recurrence Score® Result

16

The findings are applicable to women who have stage I or II node negative (N–), estrogen receptor positive (ER+) breast cancer and will be treated with 5 years of tamoxifen (tam). It is unknown whether the findings apply to other patients outside these criteria.

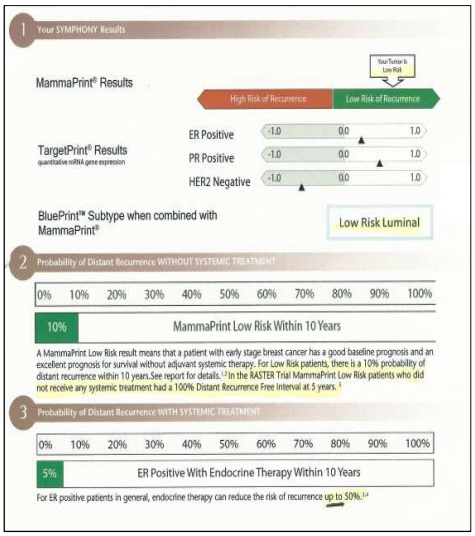
Clinical Experience: The following results are from a clinical validation study that included 651 patients from the NSABP B-20 study. The study included female patients with stage I or II, N–, ER+ breast cancer. Patients were randomized to either tam alone or tam plus CMF or MF chemotherapy. For patients in the pre-specified group with Recurrence Score results ≥ 31, the group average 10-year risks (95% CI) of distant recurrence were 40% (25%, 54%) for tam alone and 12% (6%, 18%) for tam + CMF/MF.[1]

Prediction of Chemotherapy Benefit after 5 Years of Tam, Based on the Recurrence Score Result (from NSABP B-20)

Tam Alone ——
Tam + Chemo - - - - - -

Absolute Benefit of Chemotherapy at 10 Years

Mammaprint



1 Your SYMPHONY Results

MammaPrint® Results

Your Tumor is Low Risk

High Risk of Recurrence | Low Risk of Recurrence

TargetPrint® Results
quantitative mRNA gene expression

ER Positive -1.0 0.0 1.0
PR Positive -1.0 0.0 1.0
HER2 Negative -1.0 0.0 1.0

BluePrint™ Subtype when combined with MammaPrint®: Low Risk Luminal

2 Probability of Distant Recurrence WITHOUT SYSTEMIC TREATMENT

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

10% MammaPrint Low Risk Within 10 Years

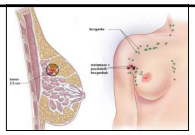
A MammaPrint Low Risk result means that a patient with early stage breast cancer has a good baseline prognosis and an excellent prognosis for survival without adjuvant systemic therapy. For Low Risk patients, there is a 10% probability of distant recurrence within 10 years. See report for details.[1,2] In the RASTER Trial MammaPrint Low Risk patients who did not receive any systemic treatment had a 100% Distant Recurrence Free Interval at 5 years.[3]

3 Probability of Distant Recurrence WITH SYSTEMIC TREATMENT

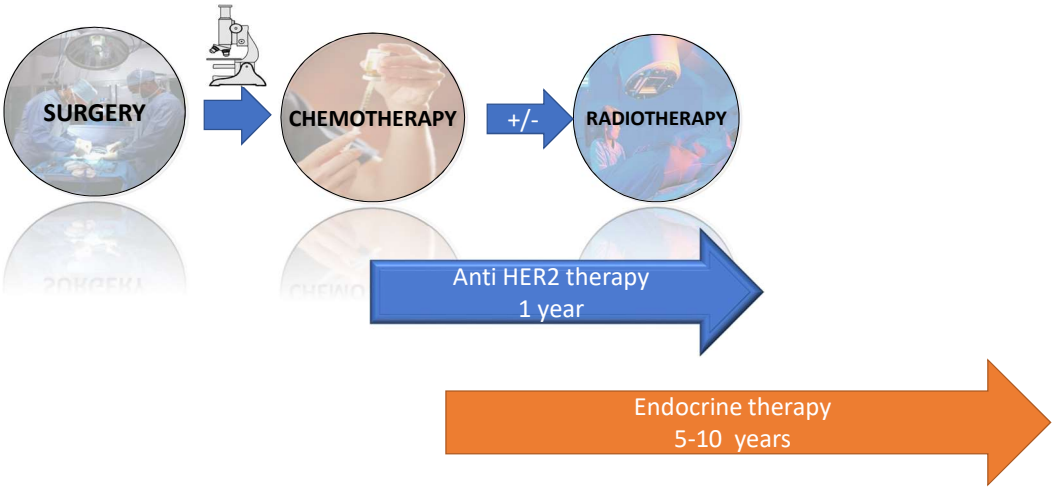
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

5% ER Positive With Endocrine Therapy Within 10 Years

For ER positive patients in general, endocrine therapy can reduce the risk of recurrence up to 50%.[3,4]



EARLY BREAST CANCER



Adjuvant therapy of triple negative BC

- CT in all pts, except *ductal, T1aNo*
  - CT with anthracyclines and taxanes (dose dense AC followed by paclitaxel every 2 weeks, dose dense AC followed by weekly paclitaxel, TC, FEC folowed by docetaxel etc.); TC, TAC, CMF

- In pts with Stage II in III neoadjuvant treatment is recommended

Adjuvant treatment of HER2+ breast cancer

CT +anti-HER2 therapy (+ ET in HR+)

- ❑CT should contain anthracyclines and taxanes;
  - a possible but not preferred choice is a combination without anthracyclines TCH (docetaxel + carboplatin + trastuzumab)
  - For pT1b,c N0, paclitaxel weekly x 12 is sufficient
  - For stage II and III, neoadjuvant CT is recommended
- ❑Anti-HER2 treatment
  - Trastuzumab +/- pertuzumab (addition of pertuzumab if positive limphnodes or negative HR
  - infusions or subcutaneous applications every 3 weeks;
    →duration: 1 year
- ❑In pts with HR+ tumors , ET after completion of CT, selection by age and menopausal status

Adjuvant therapy of HR+ (luminal) breast cancer

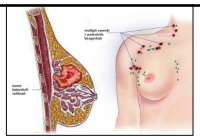
LUMINAL A	LUMINAL B
ET only	CT followed by ET
❑*Premenopausal*: tamoxifen 5 years ❑*Postmenopausal*: tamoxifen or aromatase inhibitors (AI), or both in sequence up to 5 years	❑Premenopausal: CT and then AI+ OS or tamoxifen ± OS; prolongation of ET to 10 or 15 years depending on side effects ❑ Postmenopausal: CT and then AI ± bisphosphonates; prolongation of ET to 10 or 15 years based on side effects.

Adjuvant therapy in INTERMEDIATE (HR+) BC

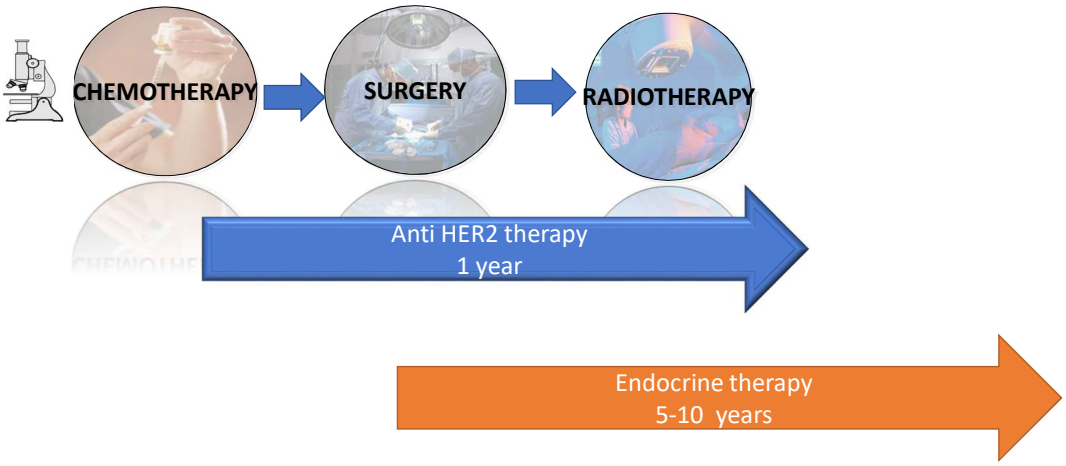
CT in majority of pts, ET in all pts

❑*Premenopausal*:
→ Tamoxifen ± OS or AI + OS in No and intermediate characteristics (gradus, proliferation, gene signature)
→ CT and then AI + OS or tamoxifen ± OS in N + and intermediate / poor characteristics (gradus, proliferation, gene signature); prolongation of HT to 10 or 15 years depending on side effects

❑*Pomenopausal*:
→ AI in NO and intermediate characteristics (gradus, proliferation, gene signature) ± bisphosphonates
→ CT and AI in N + and intermediate / poor characteristics (gradus, proliferation, gene signature) ± bisphosphonates; prolongation of HT to 10 or 15 years depending on side effects



LOCALLY ADVANCED OR TNBC/ HER2 positive, stage II or III BC



Indications for neoadjuvant CT

- ❑Inflammatory breast cancer
- ❑Triple-negative or HER2-positive stages II and III
- ❑ Luminal B with intention to deescalate surgical treatment

Diagnostic procedure before neoadjuvant CT

- ❑Core biopsy is mandatory to determine tumor characteristics
- ❑CT of the neck, chest and abdomen, bone scan
- ❑Insertion of a marker clip into the tumor before the onset of neoadjuvant CT
- ❑ Breast MRI before and after neoadjuvant CT

Choice of neoadjuvant systemic therapy

- ❑polychemotherapy: a combination of anthracyclines and taxanes is preferred(dose dense AC followed by paclitaxel every 2 weeks; dose dense AC followed by weekly paclitaxel , FEC followed by docetaxel)
- ❑ trastuzumab + pertuzumab in HER2 positive patients
- ❑capecitabine (8 cycles) is recommended in patients with triple-negative cancer where a complete response is not obtained after neoadjuvant CT,
- ❑ET in elderly patients with hormone-dependent cancer and / or contraindications for CT; 5-8 months or until the best response

Literature

- Cardoso F , Kyriakides S , Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, Zackrisson S and Senkus E, on behalf of the ESMO Guidelines Committee. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2019;30: 1194–1220.
- Waks AG, Winer EP. Breast Cancer Treatment. : A Review. *JAMA* 2019;321(3):288-300.
- Burstein HJ et al: Estimating the Benefits of Therapy for Early Stage Breast Cancer The St Gallen International Consensus Guidelines for the Primary Therapy of Early Breast Cancer 2019. Ann Oncol. 2019 Aug 2. pii: mdz235. doi: 10.1093/annonc/mdz235. [Epub ahead of print]
- https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Version 2.2019; 07/02/2019

ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY
LJUBLJANA

Case 1:
Bilateral breast cancer luminal A + luminal B (HER2+)

Author: Klara Geršak, MD
Mentor: Simona Borštnar, MD, PhD

1st Summer School in Medical Oncology
3. - 6. September 2019
LJUBLJANA

NCCN Guidelines Version 1.2018
Genetic/Familial High-Risk Assessment: Breast and Ovarian

National Comprehensive Cancer Network®

Increased risk of BC

Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast age 40 y (c,d)

Risk-reducing mastectomy: Evidence insufficient, manage based on family history

c May be modified based on family history (typically beginning screening 5–10 years earlier than the youngest diagnosis in the family but not later than stated in the table) or specific gene mutation.

d For women with mutations who are treated for breast cancer and have not had bilateral mastectomy, screening should continue as described

27.9.1967

Family history:
Mother **bilateral breast cancer** at age 50 and 52
Aunt (mother) **breast cancer** at age 39
Aunt (father) **breast cancer**

Medical history:
Healthy

Gynecological history:
Menarche at age 13
Menstrual periods not regular
No oral contraceptives
One child - at age 31

Year 2004

37 years old

Two suspicious breast lesions on mammography

↓

Core needle biopsy:
LCIS and atypical ductal hyperplasia

↓

ROLL bilateral

↓

Histology results: fibroadenoma

Year 2002

35 years old

High risk for developing breast cancer

↓

CHEK2 mutation

Regular follow ups
Mammography, breast US, MRI of the breast & visit at Medical oncologist every 6 months

Year 2014

47 years old

Right breast:
IDC 8mm (T1 N0 M0)

↓

Mastectomy bilaterally & sentinel node biopsy bilaterally; with immediate reconstruction

↓

Histology results:
Right: IDC, grade III, **10mm**, **ER 100%**, **PR 100%**, **MIB-1 25%**, **HER2 +**, **N 0/8**
Left: ILC, grade II, 6mm, **ER 100%**, **PR 100%**, **MIB-1 5%**, **HER2 -**

voting

Following treatment:

A ET + trastuzumab

B ChT + trastuzumab

C ChT + trastuzumab + ET

D ChT + trastuzumab + ET + RT

Right: IDC, grade III, **10mm**, **ER 100%, PR 100%, HER2 +, MIB-1 25%, N 0/8**

Left: ILC, grade II, **6mm**, **ER 100%, PR 100%, HER2 -, MIB-1 5%**

Year 2016

49 years old

Ovarian cyst → **laparoscopic adnexectomy bilaterally**

Side effects of hormonal therapy:

Muscle pain in arms and legs,
severe joint pain,
small foot joint stiffness,
ankle pain,
tiredness,
lower physical capacity,
hot flashes,
occasional headaches

voting

Which ChT:

A anthracylines

B taxanes

C anthracylines + taxanes

D capecitabine

Right: IDC, grade III, **10mm**, **ER 100%, PR 100%, HER2 +, MIB-1 25%, N 0/8**

Left: ILC, grade II, **6mm**, **ER 100%, PR 100%, HER2 -, MIB-1 5%**

voting

Extended Adjuvant Endocrine Therapy:

A YES

B NO

Right: IDC, grade III, **10mm**, **ER 100%, PR 100%, HER2 +, MIB-1 25%, N 0/8**

Left: ILC, grade II, **6mm**, **ER 100%, PR 100%, HER2 -, MIB-1 5%**

Year 2014

47 years old

3x **FEC-100** (5-fluorouracil, epirubicin, cyclophosphamide)

+ 3x **docetaxel**

+ **trastuzumab** (July 2014 - July 2015)

+ **tamoxifen** (from September 2014)

Year 2019

52 years old

END of **adjuvant HT** *(start: september 2014)*

Follow-ups once a year

Regular US of the heart

Lab tests repeatedly ok

Tumor marker (CA 15-3): negative

voting

Follow ups:

A LAB + tumor marker CA 15-3

B Mammography/breast US

C Clinical exam

D A+B+C

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Case 2: HR+HER2+ luminal B breast cancer

Nina Prepeluh
Simona Borštnar, PhD., MD.
Institute of Oncology Ljubljana

1st Summer School in Medical Oncology
3–6-. September 2019
LJUBLJANA

Clinical presentation

- 43- years old female
- history: lump in left breast for 6 months, otherwise healthy
- family history: cousin had uterine cancer
- gynecological history: regular menses, 4x partus, no use of contraceptive pills
- smoker (25 years, a pack a day)

Diagnostic work-up

- mammography (June 2018) – tumor formation in upper inner quadrant of left breast, 5 cm in diameter with microcalcinations; MRI- tumor formation 27x22 mm, one pathological lymph node
- core needle biopsy: IDC, grade 3, ER 100%, PgR 0%, Ki-67 15%, HER-2 positive (3+)
- staging: CT of the thorax & abdomen + bone scan – no metastases detected

TABLE 1
Criteria for staging breast tumors according to the American Joint Committee on Cancer's TNM classification[4]

	Primary tumor (T)*	Regional lymph node status (N)	Distant metastasis (M)
Stage 0	Carcinoma in situ	No evidence of cancer in nearby nodes	No
Stage I	Tumor ≤ 2 cm[1]	No evidence of cancer in nearby nodes	No
Stage IIA	No evidence of primary tumor	Metastasis to 1–3 nodes	No
	Tumor ≤ 2 cm[1]	Metastasis to 1–3 nodes	No
	Tumor > 2 cm but ≤ 5 cm	No evidence of cancer in nearby nodes	No
Stage IIB	Tumor > 2 cm but ≤ 5 cm	Metastasis to 1–3 nodes	No
	Tumor > 5 cm	No evidence of cancer in nearby nodes	No
Stage IIIA	No evidence of primary tumor	Metastasis to 4–10 nodes	No
	Tumor ≤ 2 cm[1]	Metastasis to 4–10 nodes	No
	Tumor > 2 cm but ≤ 5 cm	Metastasis to 4–10 nodes	No
	Tumor > 5 cm	Metastasis to 1–3 nodes	No
	Tumor > 5 cm	Metastasis to 4–10 nodes	No
Stage IIIB	Tumor of any size with direct extension to chest wall or skin	No evidence of cancer in nearby nodes	No
	Tumor of any size with direct extension to chest wall or skin	Metastasis to 1–3 nodes	No
	Tumor of any size with direct extension to chest wall or skin	Metastasis to 4–10 nodes	No
Stage IIIC	Any tumor designation	Metastasis to > 10 nodes	No
Stage IV	Any tumor designation	Any lymph node designation	Yes

Reference: https://www.mdedge.com/ccjm/article/94959/overview-breast-cancer-staging-and-surgical-treatment-options

What treatment regimen would you recommend to start with?

A. neoadjuvant chemotherapy (anthracyclines + taxanes) + neoadjuvant antiHER-2 therapy (trastuzumab)
B. neoadjuvant chemotherapy (anthracyclines + taxanes) + dual neoadjuvant antiHER-2 therapy (trastuzumab+ pertuzumab)
C. surgery followed by adjuvant chemotherapy + adjuvant antiHER-2 therapy
D. surgery followed by adjuvant antiHER-2 therapy

Treatment timeline

June – November 2018
NAChT (4x EC + 4x DOCE+ trastuzumab)

December 2018 – breast conserving surgery with SLNB

January 2019 - ALND

MRI breast (November 2018):
- Tumor formation of the left breast 1 cm
- US of the axilla – no suspect nodes

Pathological examination after NAChT:
- partial response – 10 mm residual tumor, R0 resection
- 2/3 positive nodes; 3 mm and 6 mm

Pathological examination
- regressive changes in 3/22 nodes

Which adjuvant therapy would you recommend?

A. anti-HER2 therapy (trastuzumab) to complete 1 year + ET (tamoxifen) + postoperative radiotherapy
B. anti-HER2 therapy (trastuzumab) to complete 1 year + ET (goserelin/oophorectomy with AI) + postoperative radiotherapy
C. anti-HER2 therapy (trastuzumab) to complete 1 year followed by adjuvant neratinib
D. anti-HER2 therapy (trastuzumab) to complete 1 year + ET (tamoxifen)
E. dual anti-HER2 therapy (trastuzumab + pertuzumab) to complete 1 year + ET (tamoxifen) + postoperative radiotherapy

Treatment timeline (part 2)

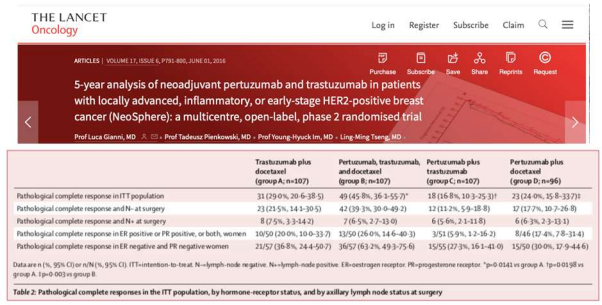
February 2019 – started adjuvant ET with tamoxifen and continued with trastuzumab

March – May 2019 postoperative radiotherapy: 57 Gy in 25 fractions

September 2019 – last trastuzumab administration, continuing treatment with tamoxifen

august 2019:
- no symptoms or signs of relapse, no mayor AE of the therapy

Clinical trials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ARTICLES | VOLUME 17, ISSUE 6, P791-800, JUNE 01, 2016

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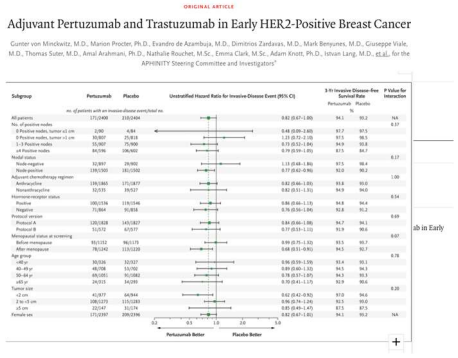
5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial

Prof Luca Gianni, MD • Prof Tadeusz Pienkowski, MD • Prof Young-Hyuck Im, MD • Ling-Ming Tseng, MD

	Trastuzumab plus docetaxel (group A; n=107)	Pertuzumab, trastuzumab, and docetaxel (group B; n=107)	Pertuzumab plus trastuzumab (group C; n=107)	Pertuzumab plus docetaxel (group D; n=96)
Pathological complete response in ITT population	31 (29·0%, 20·6–38·5)	49 (45·8%, 36·1–55·7)*	18 (16·8%, 10·3–25·3)†	23 (24·0%, 15·8–33·7)†
Pathological complete response and N+ at surgery	7 (23·5%, 14·3–30·5)	47 (39·3%, 30·0–49·2)	12 (11·2%, 5·9–18·8)	17 (17·7%, 10·7–26·8)
Pathological complete response and N+ at surgery	8 (7·5%, 3·3–14·2)	7 (6·5%, 2·7–13·0)	6 (5·6%, 2·1–11·8)	6 (6·3%, 2·3–13·1)
Pathological complete response in ER positive or PR positive, or both, women	10/50 (20·0%, 10·0–33·7)	13/50 (26·0%, 14·6–40·3)	3/51 (5·9%, 1·2–16·2)	8/46 (17·4%, 7·8–31·4)
Pathological complete response in ER negative and PR negative women	21/57 (36·8%, 24·4–50·7)	36/57 (63·2%, 49·3–75·6)	15/55 (27·3%, 16·1–41·0)	15/50 (30·0%, 17·9–44·6)

Data are n (%, 95% CI) or n/N (%, 95% CI). ITT=intention-to-treat. N−=lymph-node negative. N+=lymph-node positive. ER=oestrogen receptor. PR=progesterone receptor. *p=0·0141 vs group A. †p=0·0198 vs group A. ‡p=0·003 vs group B.

Table 2: Pathological complete responses in the ITT population, by hormone-receptor status, and by axillary lymph node status at surgery

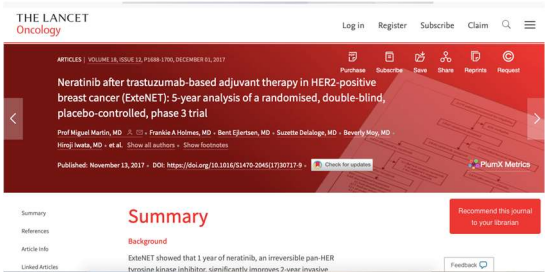

ORIGINAL ARTICLE

Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer

Gunter von Minckwitz, M.D., Marion Procter, Ph.D., Evandro de Azambuja, M.D., Dimitrios Zardavas, M.D., Mark Benyunes, M.D., Giuseppe Viale, M.D., Thomas Suter, M.D., Amal Arahmani, Ph.D., Nathalie Rouchet, M.Sc., Emma Clark, M.Sc., Adam Knott, Ph.D., Istvan Lang, M.D., et al., for the APHINITY Steering Committee and Investigators*

Pertuzumab Better | Placebo Better

There is more to come…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ARTICLES | VOLUME 18, ISSUE 12, P1688-1700, DECEMBER 01, 2017

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Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial

Prof Miguel Martin, MD • Frankie A Holmes, MD • Bent Ejlertsen, MD • Suzette Delaloge, MD • Beverly Moy, MD • Hiroji Iwata, MD • et al. Show all authors • Show footnotes

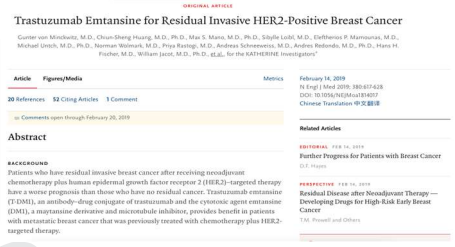
Published: November 13, 2017 • DOI: https://doi.org/10.1016/S1470-2045(17)30717-9 • Check for updates

PlumX Metrics

Summary

Background

ExteNET showed that 1 year of neratinib, an irreversible pan-HER tyrosine kinase inhibitor, significantly improves 2-year invasive


ORIGINAL ARTICLES

Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer

Gunter von Minckwitz, M.D., Chiun-Sheng Huang, M.D., Ph.D., Max S. Mano, M.D., Ph.D., Sibylle Loibl, M.D., Eleftherios P. Mamounas, M.D., Michael Untch, M.D., Ph.D., Norman Wolmark, M.D., Priya Rastogi, M.D., Andreas Schneeweiss, M.D., Andres Redondo, M.D., Ph.D., Hans H. Fischer, M.D., William Jacot, M.D., Ph.D., et al., for the KATHERINE Investigators*

Article | Figures/Media | Metrics

20 References 52 Citing Articles 3 Comment

Comments open through February 20, 2019

Abstract

BACKGROUND

Patients who have residual invasive breast cancer after receiving neoadjuvant chemotherapy plus human epidermal growth factor receptor 2 (HER2)–targeted therapy have a worse prognosis than those who have no residual cancer. Trastuzumab emtansine (T-DM1), an antibody–drug conjugate of trastuzumab and the cytotoxic agent emtansine (DM1), a maytansine derivative and microtubule inhibitor, provides benefit in patients with metastatic breast cancer that was previously treated with chemotherapy plus HER2-targeted therapy.

February 14, 2019

N Engl J Med 2019; 380:617-628

DOI: 10.1056/NEJMoa1814017

Chinese Translation 中文翻译

Related Articles

EDITORIAL FEB 14, 2019

Further Progress for Patients with Breast Cancer

D.F. Hayes

PERSPECTIVE FEB 14, 2019

Residual Disease after Neoadjuvant Therapy — Developing Drugs for High-Risk Early Breast Cancer

T.M. Prowell and Others

ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY
LJUBLJANA

Case 3:
Early TNBC

Author: Klara Geršak, MD
Mentor: Simona Borštnar, MD, PhD

1st Summer School in Medical Oncology
3. - 6. September 2019
LJUBLJANA

Born: 4.11.1990

Family history of cancer:
Aunt - cancer of the **larynx** at age 67 (father's side)
Grandfather - **breast** cancer at age 60
Aunt - **breast** cancer at age 80

Hashimoto thyroiditis
Euthyrox 50 mcg/day

Menarche at age 12
Menstrual periods regular
Oral **contraceptive** use for 9 years
0 pregnancies, 0 abortions

Medical doctor (just started internship), lives with her family

Year 2018:

27 years old

LEFT breast

Self examination
Upper quadrants
Fine needle aspiration of the breast tumor (US 1.4x1 cm) and lymph node in the left axilla (US 7 mm)
Cytology results: adenocarcinoma and metastasis of the adenocarcinoma in the lymph node

Core needle biopsy 5.7.2018:
IDC, poorly differentiated, high nuclear grade,
ER 0%, PR 0%, MIB-1 around 30%, HER-2 neg.

Tumor size - clinically:
1.5 x 1 cm
Clinically no lymph node in the axilla.

VAP
Genetic counselling and testing

Year 2018:

27 years old

LEFT breast

Self examination
Upper quadrants
Fine needle aspiration of the breast tumor (US 1.4x1 cm) and lymph node in the left axilla (US 7 mm)
Cytology results: adenocarcinoma and metastasis of the adenocarcinoma in the lymph node

Core needle biopsy 5.7.2018:
IDC, poorly differentiated, high nuclear grade,
ER 0%, PR 0%, MIB-1 around 30%, HER-2 neg.

BRCA 2 mutation

Tumor size - clinically:
1.5 x 1 cm
Clinically no lymph node in the axilla.

VAP
Genetic counselling and testing

voting

How to treat:

A NACT + surgery

B surgery + adjuvant ChT

US 1.4x1 cm

lymph node in the left axilla (US 7 mm)

IDC, poorly differentiated, high nuclear grade,
ER 0%, PR 0%, MIB-1 around 30%, HER-2 neg

voting

Which ChT:

A dose dense anthracyclines+taxanes (AC+PACLI)

B (F)EC+DOCE

C capecitabine

US 1.4x1 cm

lymph node in the left axilla (US 7 mm)

IDC, poorly differentiated, high nuclear grade,
ER 0%, PR 0%, MIB-1 around 30%, HER-2 neg

NEOADJUVANT SYSTEMIC THERAPY

4x AC (DOXORUBICIN+CYCLOPHOSPHAMIDE)

+

4x PAKLITAKSEL

+ pegfilgrastim

DOSE

DENSE

After 2. Cycles of the therapy: no tumor clinically

16.11.2018 OPERATION

27 years old

LEFT: Subcutaneous mastectomy with axillary lymph node dissection + immediate reconstruction

RIGHT: *prophylactic mastectomy* + immediate reconstruction

Pathohistological results:

Residual IDC and DCIS,
partial response to therapy - **10-50% residual tumor.**
No vascular invasion. No perineural invasion. Surgical margins clear.
Nodal status 2/24 - 1mm & 5mm - without extracapsular growth.

voting

Following treatment:

A RT

B capecitabine

C RT + capecitabine

partial response to therapy

nodal status 2/24 - 1mm & 5mm - without extracapsular growth

US 14 x 10 mm

lymph node in the left axilla (US 7 mm)

IDC, poorly differentiated, high nuclear grade, ER 0%, PR 0%, MIB-1 around 30%, HER-2 neg

28 years old

Adjuvant RADIATION therapy

From 14.1.- 20.2.2019
(+ parasternal lymph nodes)

28 years old

25.2.2019 **adjuvant CHEMOTHERAPY**

Capecitabine 2150 mg/12 hours, 14 days
+ goserelin 3.6 mg sc

6th, 7th and 8th cycle 75% dose - because of hematotoxicity

Last visit: 16.8.2019

voting

Expected 10-year survival:

A More than 90%

B 80-89%

C 70-79%

US 14 x 10 mm

lymph node in the left axilla (US 7 mm)

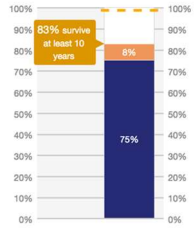
IDC, poorly differentiated, high nuclear grade, ER 0%, PR 0%, MIB-1 around 30%, HER-2 neg

partial response to therapy

nodal status 2/24 - 1mm & 5mm - without extracapsular growth

Overall survival

This chart shows the percentage of women surviving 10 years after surgery.



Survival rate excluding deaths from breast cancer.

Additional benefit of chemotherapy is 8% at 10 years.

Surgery only survival is 75% at 10 years.

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INSTITUTE OF ONCOLOGY
LJUBLJANA

Case 4: First-line ribociclib in primary metastatic hormone receptor-positive breast cancer

Author: Urška Rugelj, MD
Mentor: Simona Borštnar, MD, PhD

1st Summer School in Medical Oncology
3. - 6. September 2019
LJUBLJANA

Clinical case

- 43-year-old premenopausal woman
- No comorbidities
- Medication: antihistamines due to atopy
- Family history negative for malignancy
- First visit in June 2017
  - Patient presented with a lump 5x4cm lump in the upper inner quadrant of the left breast
  - No skin or areola abnormalities
  - No enlarged lymph nodes
  - ECOG: 0

Initial assessment

- Imaging:
  - Mammography – structural abnormality in the left breast
  - Magnetic resonance imaging of the left breast: tumor on the border of upper quadrants 50×35 mm, 2 other foci in the upper and lower inner quadrant 30 and 35 mm, pathological axillary lymph nodes with enlarged capsule – the largest 6 mm in diameter
  - Bone scan: no signs of osteoblastic lesions
  - Ultrasound of the abdomen: no signs of metastases
  - Chest X-ray: no signs of metastases
- Cytological puncture of the tumor: adenocarcinoma
- Ultrasound guided cytological puncture of the axillary lymph node: metastasis of the adenocarcinoma

- Diagnosis: adenocarcinoma of the left breast with positive ipsilateral axillary lymph nodes

Core needle biopsy – pathology report

- Biopsy
  - Core needle biopsy
  - Histopathology: ILC
- Biomarkers
  - HER2–, PgR 95%, ER 100%, Ki67 5–10%
- Gene signature
  - Not done

- Luminal A like disease

Initial treatment and final pathology

- Surgery:
  - Radical mastectomy and axillary lymph node dissection with immediate reconstruction with DIEP flap

- Definitive histology
  - Invasive lobular carcinoma, 50 mm in largest diameter, with foci of lobular carcinoma in situ, grade 2, mitosis 2, lymphovascular invasion present
  - 25/28 axillary lymph nodes positive, the largest metastasis measuring
    18 mm with extension outside of the capsule and infiltrating the surrounding adipose tissue

voting

What additional treatment would you recomend?

A. Adjuvant endocrine therapy

A. Adjuvant endocrine therapy and radiotherapy

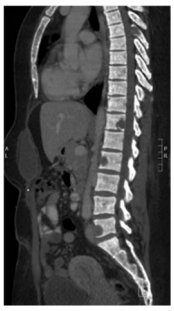
A. Adjuvant chemotherapy and endocrine therapy

A. Adjuvant chemotherapy, endocrine therapy and radiotherapy

- Early breast cancer
- Invasive lobular carcinoma
- pT2N3aMx
- Stage IIIC
- HR positive, Her-2 negative, grade II, MIB1 10-15%

New symptoms

- Before chemotherapy was started new onset of pain with deterioration of performance status from 0 to 1 was observed
- Additional bone scan – September 2018
  - No changes from the preoperative scan in June 2018 – most likely degenerative changes in both shoulders and hips
- CT of the chest and abdomen – September 2018
  - Diffuse osteolytic bone metastases, no signs of metastases elsewhere



voting

What would you do now?

A. Continue with the initial treatment plan (ChT, ET, RT)
B. Ovarian function suppression and ET with AI
C. Ovarian function suppression and ET with tamoxifen
D. Ovarian function suppression and ET with AI and CD4/6 inh
E. Ovarian function suppression and ET with tamoxifen and CD4/6 inh
F. Chemotherapy

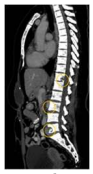
primary metastatic HR+/HER2– breast cancer, bone only

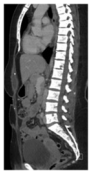
First line treatment

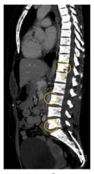
- Ribociclib 600 mg once daily (OD) for 21 days, then 7 days off
- Letrozole 2.5 mg OD continuously
- Goserelin 3.6 mg subcutaneously monthly
- Denosumab 120 mg subcutaneously monthly
- Monitoring strategy
  - Complete blood count (CBC), liver tests, electrolytes and electrocardiogram – every 14 days for the first 2 or 3 cycles
  - CBC, liver tests, electrolytes monthly
- Supportive treatment:
  - Analgesia with paracetamol/tramadol combination, later de-escalation to a non-steroidal anti-inflammatory drug
  - Calcium carbonate, vitamin D due to bone antiresorptive agent

Treatment - cont.

- Patient responded well to therapy, no major adverse effects were noted, no treatment delays, the pain improved
- Improvement in ECOG from 1 to 0 was noted
- Quality of life was improved
- The best response is stable disease. The duration of response is currently 20 months


Month 3


Month 6


Month 9

Conclusion

- Patient started her treatment of an early breast cancer
- Bone metastases were found after surgery when new symptoms were present
- Treatment plan was changed from adjuvant chemotherapy, followed by endocrinal therapy and radiotherapy to treatment of primary metastatic HR+/HER2– breast cancer with a combination of hormonal therapy and a CDK 4/6 inhibitor

Metastatic breast cancer

1st Summer School in medical oncology – Standards and open questions

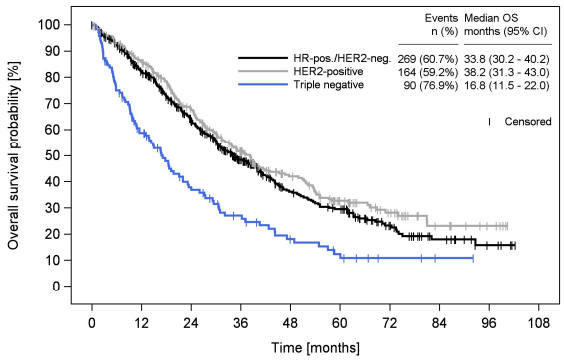
Domen Ribnikar, MD, Medical Oncology staff
Institute of Oncology Ljubljana
Department of Medical Oncology
Ljubljana, September 5th 2019

TMK

Tumor Register Mammakarzinom

Prospective German TMK cohort study

Overall survival according to subtype



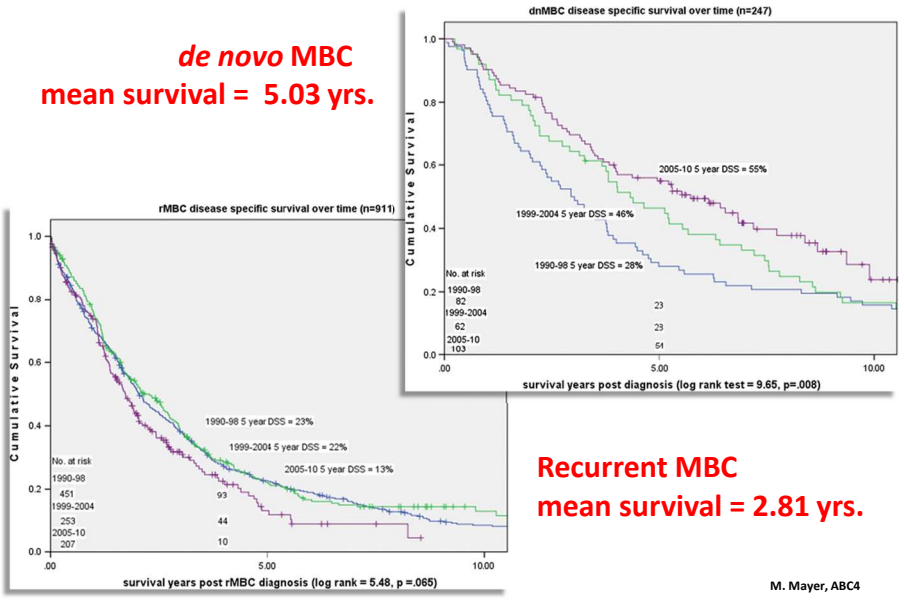
Number at risk

HR-pos./HER2-neg.	443	344	239	147	83	65	31	14	5	0
HER2-positive	277	226	163	111	74	46	26	11	5	0
Triple negative	117	63	37	23	13	8	3	1	0	

Fietz, T., Tesch, H., Rauh, J., Boller, E., Kruggel, L., Jänicke, M., Marschner, N., 2017. Palliative systemic therapy and overall survival of 1,395 patients with advanced breast cancer – Results from the prospective German TMK cohort study. The Breast 34, 122–130, 2017

Prognosis of de novo & recurrent MBC diverges over time

***de novo* MBC**
mean survival = 5.03 yrs.



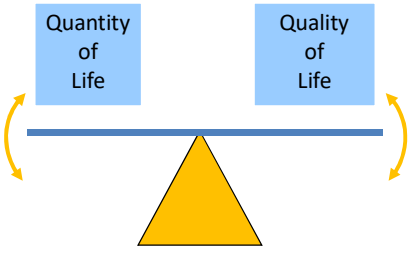
Recurrent MBC
mean survival = 2.81 yrs.

M. Mayer, ABC4

Goals of the Treatment in MBC

- **Balancing treatment efficacy and toxicity is the main objective**

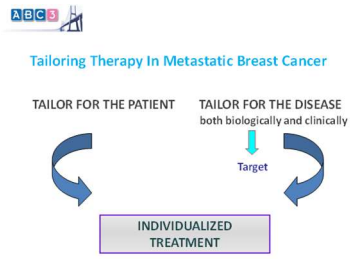
- **Goals of treatment:**
  - **Improve survival** *(very few agents achieve it!)*
  - **Delay disease progression**
  - **Prolong duration of response**
  - **Palliate symptoms**
  - **Improve or maintain quality of life**
  - **Transform into a chronic disease**



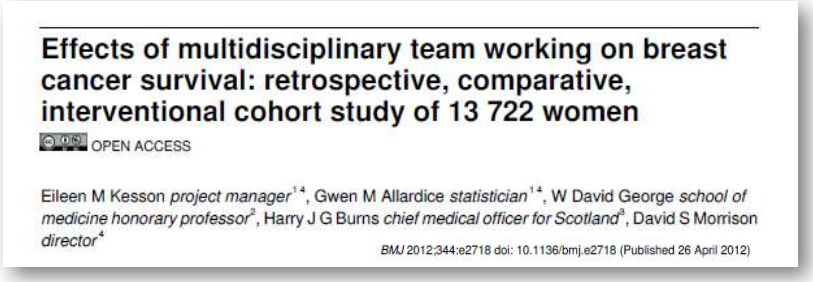
TREATMENT TAILORING IN MBC

Treatment choice should take into account at least these factors:

HR & HER-2 status,
previous therapies and their toxicities, disease-free interval,
tumor burden (defined as number and site of metastases),
biological age, performance status, co-morbidities (including organ dysfunctions),
menopausal status (for ET),
need for a rapid disease/symptom control,
socio-economic and psychological factors,
available therapies in the patient's country and patient preference!



The management of MBC is complex and, therefore, involvement of all appropriate specialties in a multidisciplinary team (including but not restricted to medical, radiation, surgical oncologists, imaging experts, pathologists, gynecologists, psycho-oncologists, social workers, nurses and palliative care specialists), is crucial.



Effects of multidisciplinary team working on breast cancer survival: retrospective, comparative, interventional cohort study of 13 722 women

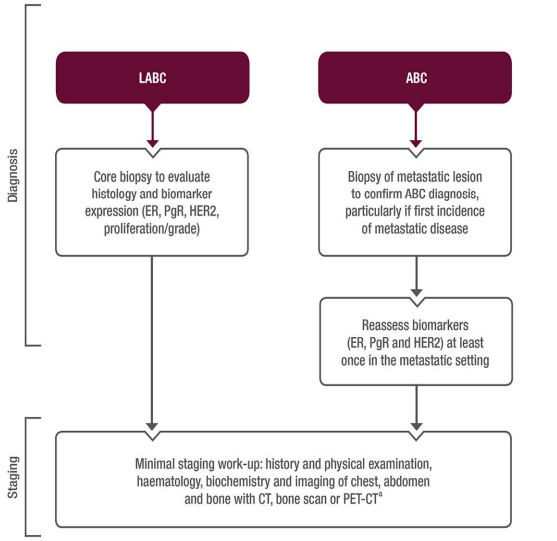
OPEN ACCESS

Eileen M Kesson *project manager*[1 4], Gwen M Allardice *statistician*[1 4], W David George *school of medicine honorary professor*[2], Harry J G Burns *chief medical officer for Scotland*[3], David S Morrison *director*[4]

BMJ 2012;344:e2718 doi: 10.1136/bmj.e2718 (Published 26 April 2012)

CLINICAL PRACTICE GUIDELINES

ABC diagnostic work-up and staging



*Discuss indications. Brain MRI not indicated unless there are symptoms

ESMO

LUMINAL TUMOURS = HETEROGENEOUS GROUP

- The principal characteristic of the luminal group is the **luminal expression signature**, composed of ***ESR1*, *GATA3*, *FOXA1*, *XBP1*, and *cMYB***
  - the most frequent mutations in the **luminal A** subtype are ***PIK3CA* (45%),** *MAP3K1* (13%), *GATA3* (13%), *TP53* (12%), and *CDH1* (9%)
  - the most frequent mutations in **luminal B** tumors are ***TP53* (29%), *PIK3CA* (29%)**, *GATA3* (13%), and *TTN* (12%)
- In addition to *TP53* mutations, several other events may intervene in other steps of the same pathway, including *ATM* loss and *MDM2* amplification
- **ESR1** mutations (up to 19%) after **AI treatment => resistance**

Courtesy F. Penault-Llorca

Mechanisms of *De Novo* & Acquired Endocrine Resistance

De Novo **ET Resistance** ⟷ **Acquired ET Resistance**

- The lost/inactivation of ER/ER pathway
- Activation of PI3K/AKT/mTOR pathway
- Activation of the growth factor or HER pathway activation

1. Osborne CK, et al. *Ann Rev Med*. 2011;62:233-247; 2. Arpino G, et al. *Endocr Rev*. 2008;29:217-233; 3. Shou J, et al. *J Natl Cancer Inst*. 2004;96(12):926-935; 4. Chung YL, et al. *Int J Cancer*. 2002;97:306-312; 5. Meng S, et al. *Proc Natl Acad Sci USA*. 2004;101:9393-9398; 6. Nicholson RI, et al. *Endocr Relat Cancer*. 2004;11:623-641; 7. Gee JM, et al. *Endocrinology*. 2003;144:5105-5117; 8. Knowlden JM, et al. *Endocrinology*. 2005;146:4609-4618; 9. Miller W, et al. AARC Special Conference: Targeting PI3K/mTOR Signaling in Cancer; 2011. Abstract A09.

HOW TO TACKLE HETEROGENEITY OF LUMINAL-LIKE MBC?
Are there ready-to-use (bio)markers to individualize treatment?

- None ready for clinical practice yet!
- So, how do we choose?

HOW TO TREAT ER+/HER-2 neg (LUMINAL) MBC:

MAIN QUESTIONS:

1. Do we need Chemotherapy (CT)?
2. If Endocrine Therapy (ET) which agent?
3. Is a targeted agent also necessary or is ET alone sufficient?
4. If CT: combination vs. sequential monotherapy?
5. If CT: which agent(s)?

ER POSITIVE / HER-2 NEGATIVE MBC

Endocrine therapy (ET) is the preferred option for hormone receptor positive disease, even in the presence of visceral disease, unless there is visceral crisis or concern/proof of endocrine resistance.

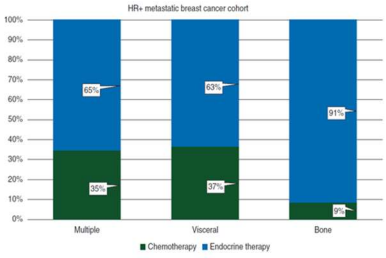
ALL guidelines are in agreement for this recommendation

In real life, one-quarter of patients with hormone receptor-positive metastatic breast cancer receive chemotherapy as initial palliative therapy: a study of the Southeast Netherlands Breast Cancer Consortium

D. J. A. Lobbezoo[1,2], R. J. W. van Kampen[1], A. C. Voogd[1,3], M. W. Dercksen[2], F. van den Berkmortel[4], T. J. Smilde[5], A. J. van de Wouw[6], F. P. J. Peters[7], J. M. G. H. van Riel[8], N. A. J. B. Peters[9], M. de Boer[1], P. G. M. Peer[10] & V. C. G. Tjan-Heijnen[1]*

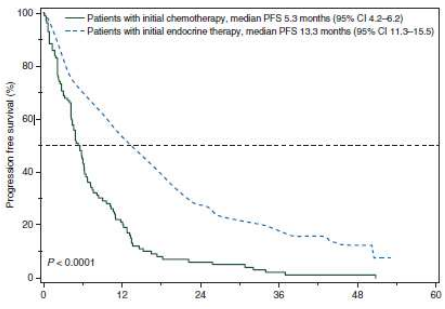
[1]GROW—School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht; [2]Department of Internal Medicine, Máxima Medical Center, Veldhoven; [3]Netherlands Comprehensive Cancer Organisation, Utrecht; [4]Department of Internal Medicine, Atrium-Orbis Hearlen, Heerlen; [5]Department of Medical Oncology, Jeroen Bosch Hospital, Den Bosch; [6]Department of Internal Medicine, VieCuri Medical Center, Venlo; [7]Department of Internal Medicine, Ahrum-Orbis Sittard, Sittard; [8]Department of Internal Medicine, St Elisabeth Hospital, Tilburg; [9]Department of Internal Medicine, St Jans Hospital, Weert; [10]Department for Health Evidence, Radboud University Medical Center, Nijmegen, The Netherlands

Received 24 May 2015; revised 28 August 2015 and 14 October 2015; accepted 26 October 2015

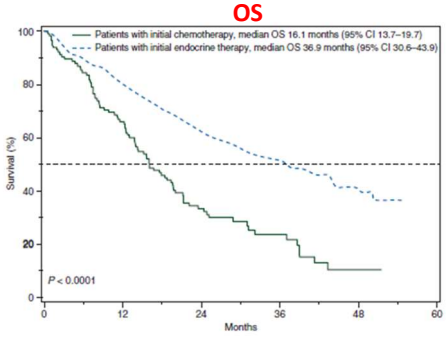


Starting with ET vs. Starting with CT

PFS

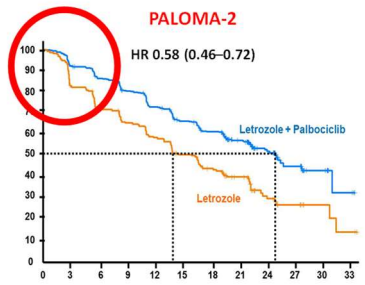


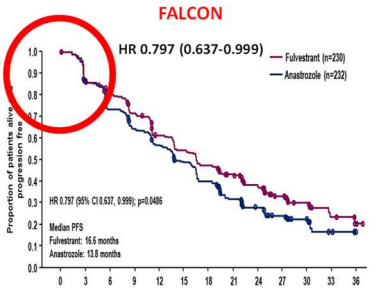
OS



MAIN CHALLENGE:
Identify small percentage of "fast progressors"

First line endocrine therapy: FALCON or PALOMA-2?





Finn et al. ESMO 2016, LBA-15; Ellis et al. ESMO 2016, LBA-14

Courtesy Peter Schmid, ESMO 2016, Discussant

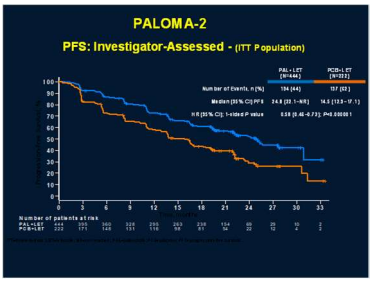
ER POSITIVE / HER-2 NEGATIVE MBC

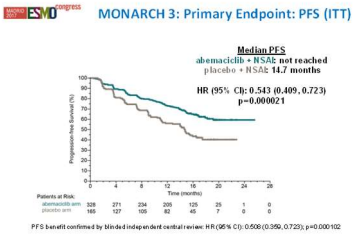
The addition of a CDK4/6 inhibitor to an aromatase inhibitor, in patients naïve or pre-exposed to ET, provided a significant improvement in median PFS (~10 months), with an acceptable toxicity profile, and is therefore one of the preferred treatment options*. Patients relapsing < 12 months from the end of adjuvant AI were not included in the published studies and may not be suitable for this combination.

OS results are still awaited. QoL was comparable to that with ET alone.

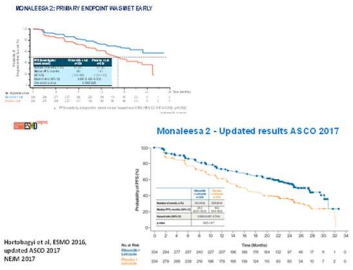
* for pre and peri with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women

1st Line CDK 4/6 INHIBITORS: EFFICACY

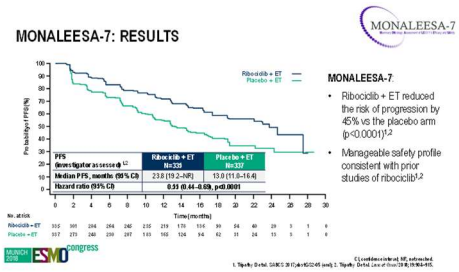




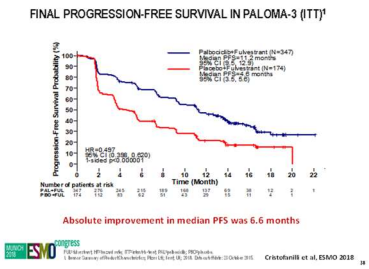
Di Leo et al, ESMO 2017



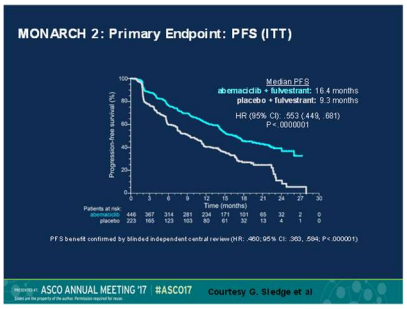
Hortobagyi et al, ESMO 2016, updated ASCO 2017
NEJM 2017



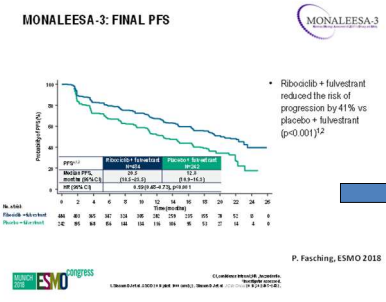
2nd Line CDK 4/6 INHIBITORS: EFFICACY



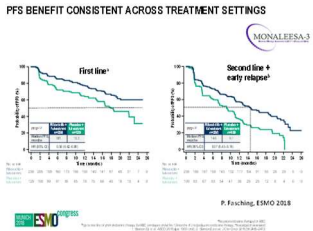
Cristofanilli et al, ESMO 2018



Courtesy G. Sledge et al

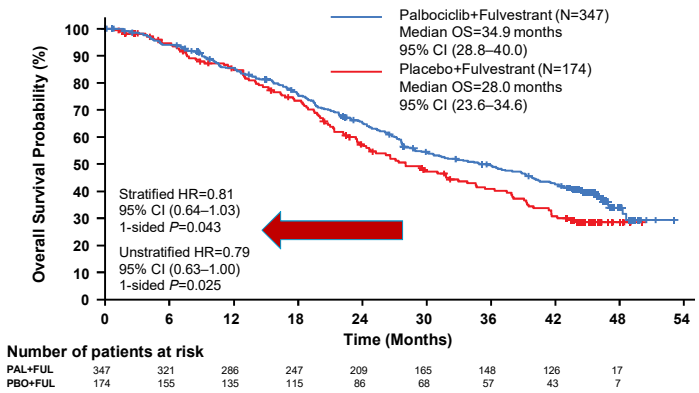


P. Fasching, ESMO 2018



P. Fasching, ESMO 2018

OVERALL SURVIVAL IN PALOMA-3 (ITT)



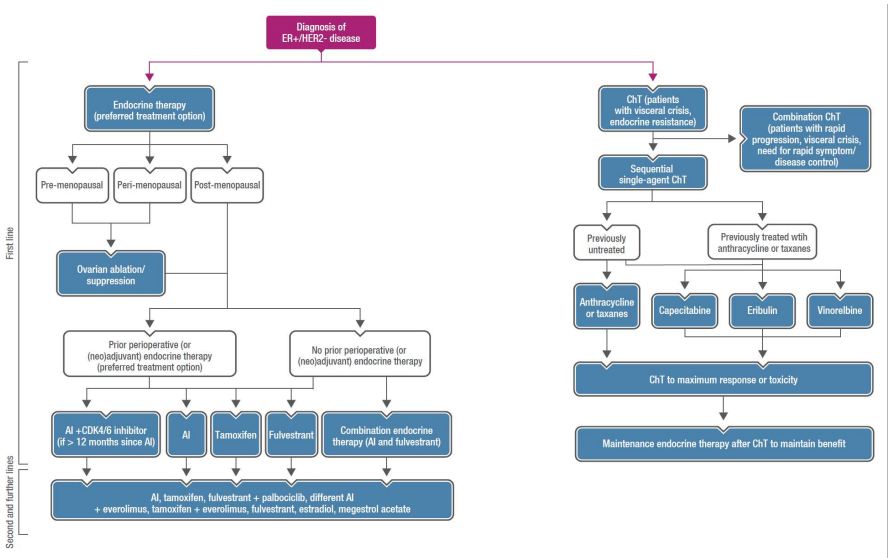
Absolute improvement in median OS was 6.9 months

BUT

NOT STATISTICALLY SIGNIFICANT

Cristofanilli et al, ESMO 2018

MANAGEMENT OF LUMINAL MBC

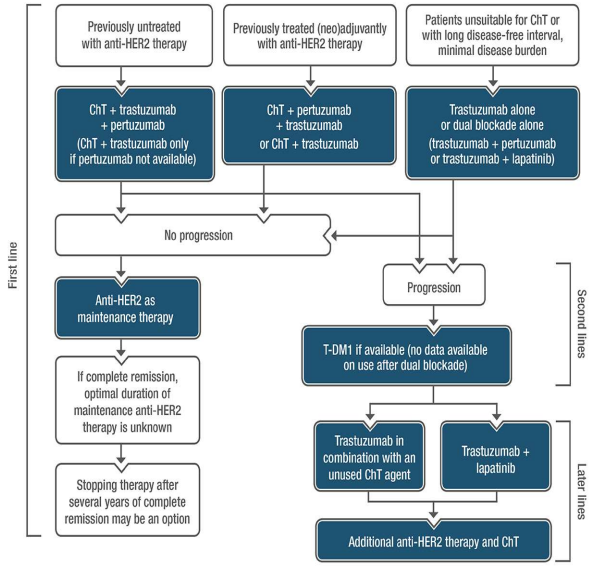


ABC, advanced breast cancer; AI, aromatase inhibitor; ChT, chemotherapy; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2

F Cardoso et al, Annals of Oncology 2018

CLINICAL PRACTICE GUIDELINES

Treatment of ER-negative / HER2-positive ABC

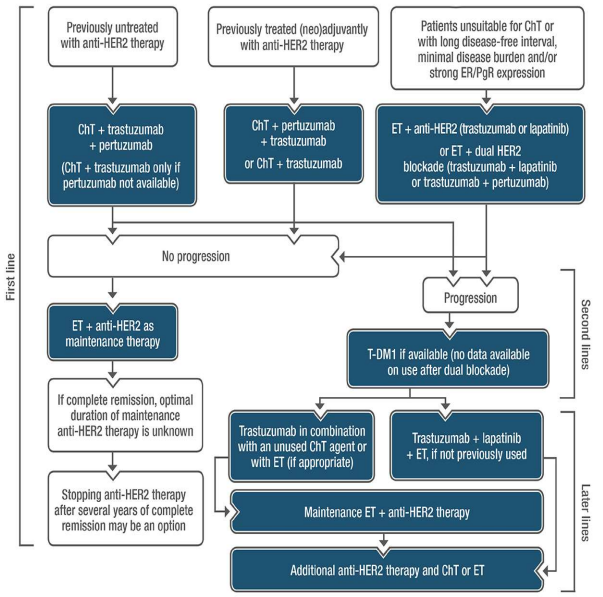


Note: Include in clinical trials when available

ESMO

CLINICAL PRACTICE GUIDELINES

Treatment of ER-positive / HER2-positive ABC



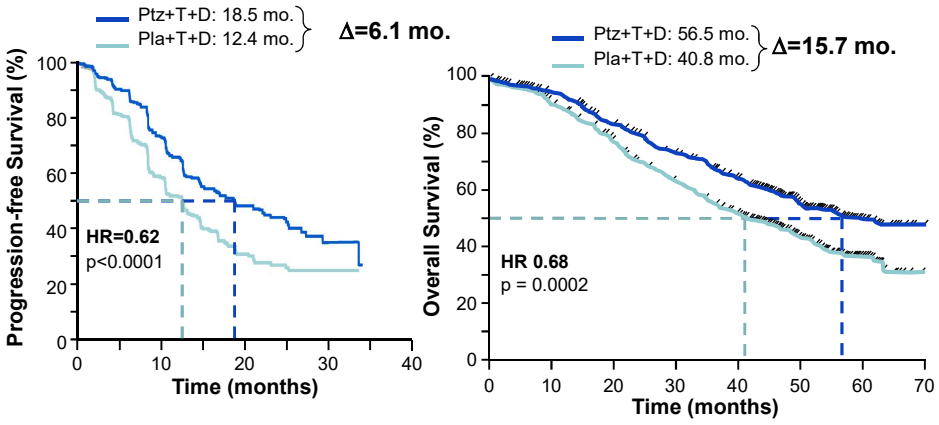
Note: Include in clinical trials when available

ESMO

CLEOPATRA: *Median PFS and OS*

CAUTION!!!!

Only 21% -26% pts had previously received (neo)adjuvant trastuzumab



Baselga et al., NEJM 2012., Swain et al., NEJM, 2015.

HER-2 POSITIVE MBC: 2nd line and beyond

After 1st line trastuzumab-based therapy, T-DM1 provides superior efficacy relative to other HER-2-based therapies in the 2nd line (vs. lapatinib + capecitabine) and beyond (vs. treatment of physician's choice).

T-DM1 should be preferred in patients who have progressed through at least 1 line of trastuzumab-based therapy, because it provides an OS benefit.

TNBC: CHEMOTHERAPY (general)

Both combination and sequential single agent CT are reasonable options. Based on the available data, we recommend sequential monotherapy as the preferred choice for MBC.

Combination CT should be reserved for patients with rapid clinical progression, life-threatening visceral metastases, or need for rapid symptom and/or disease control.

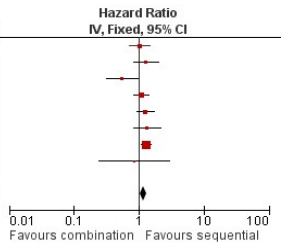
ALL guidelines are in agreement for this recommendation

Cochrane meta-analysis of Combination vs. Sequential monoCT for MBC

Progression-free survival (all trials)

Study or Subgroup	log[Hazard Ratio]	SE	Combination Total	Sequential Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Alba 2004	0.0296	0.1827	69	75	10.7%	1.03 [0.72, 1.47]
Baker 1974	0.239	0.2295	46	30	6.8%	1.27 [0.81, 1.99]
Beslija 2006	-0.6033	0.2865	50	50	4.3%	0.55 [0.31, 0.96]
Conte 2004	0.0862	0.139	106	92	18.5%	1.09 [0.83, 1.43]
Fountzilas 2001	0.2151	0.1579	90	93	14.3%	1.24 [0.91, 1.69]
Park 2010	0.2776	0.2429	41	40	6.0%	1.32 [0.82, 2.12]
Sledge 2003	0.2469	0.0962	230	453	38.5%	1.28 [1.06, 1.55]
Tomova 2010	-0.1625	0.6415	46	53	0.9%	0.85 [0.24, 2.99]
Total (95% CI)			**678**	**886**	**100.0%**	**1.16 [1.03, 1.31]**

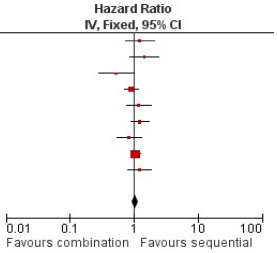
Heterogeneity: Chi² = 9.41, df = 7 (P = 0.22); I² = 26%
Test for overall effect: Z = 2.52 (P = 0.01)



Overall survival (all trials)

Study or Subgroup	log[Hazard Ratio]	SE	Combination Total	Sequential Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Alba 2004	0.2151	0.2634	69	75	4.5%	1.24 [0.74, 2.08]
Baker 1974	0.3716	0.2606	46	30	4.6%	1.45 [0.87, 2.42]
Beslija 2006	-0.6387	0.3182	50	50	3.1%	0.53 [0.28, 0.99]
Chlebowski 1989	-0.1054	0.1282	129	93	19.2%	0.90 [0.70, 1.16]
Conte 2004	0.174	0.2355	106	92	5.7%	1.19 [0.75, 1.89]
Fountzilas 2001	0.1989	0.1667	90	93	11.3%	1.22 [0.88, 1.69]
Park 2010	-0.1744	0.235	41	40	5.7%	0.84 [0.53, 1.33]
Sledge 2003	0.0488	0.0901	230	453	38.8%	1.05 [0.88, 1.25]
Tomova 2010	0.1989	0.211	46	53	7.1%	1.22 [0.81, 1.84]
Total (95% CI)			**807**	**979**	**100.0%**	**1.04 [0.93, 1.16]**

Heterogeneity: Chi² = 10.54, df = 8 (P = 0.23); I² = 24%
Test for overall effect: Z = 0.76 (P = 0.45)

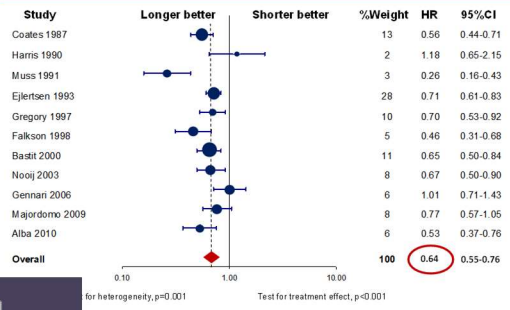


Dear RF et al. Combination vs. sequential single agent CT for MBC (Review) 2013

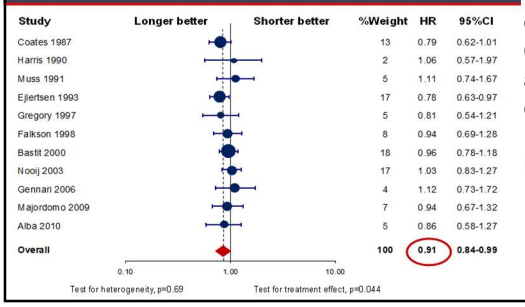
Optimal Duration of Chemotherapy?

- Longer CT duration associated with :
- significant improvement in PFS (HR 0.64; 95% CI 0.55 – 0.76)
- significant improvement in OS (HR 0.91; 95% CI 0.84-0.99)

Results: Progression Free Survival



Results: Overall Survival



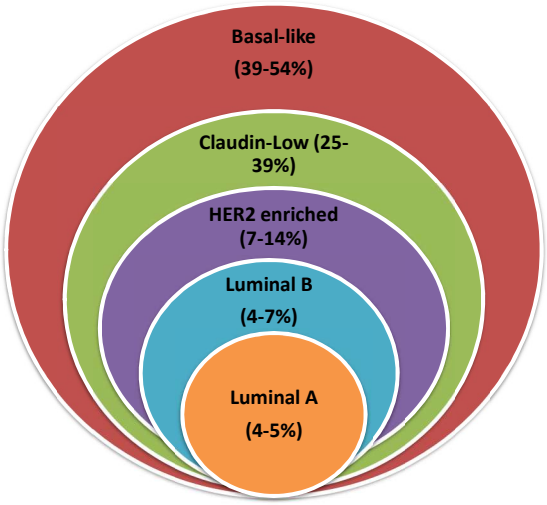
These results provide support to the clinical approach of prolonging 1st line CT in the absence of significant toxicity and disease progression (when CT is the only option…)

Role of biologics, HT, metronomic CT !?!

Gennari et al, J Clin Oncol 2011

Heterogeneity of TNBC:

Data from the UNC337, NKI1295, MDACC133 databases



Basal-like
- Up to 19% are ER+

Claudin-low
- Up to 33% are ER+

Pratt et al, Breast Cancer Res, 2010

Courtesy H. Rugo, ASCO 2011

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INSTITUTE OF ONCOLOGY
LJUBLJANA

Case 5: Metastatic HR+ BC with visceral crisis

Authors: Luka Dobovišek, MD; Anja Kovač, MD
Mentor: Simona Borštnar, MD, PhD

1st Summer School in Medical Oncology
3. - 6. September 2019
LJUBLJANA

CLINICAL PRESENTATION

- 51-year old female (March 2017)
- 2 months history of dry cough, pleuritic and abdominal pain
- Other medical conditions: none
- Gynecological history: regular menses, 1x partus, 1x abortus
- PS 2, jaundice, palpable mass left breast (5 cm), enlarged liver (reaching the umbilical line)
- CT (thorax, abdomen): multiple confluating liver lesions, tumour left breast (35 mm), tumor in the left ovary

TUMOR BIOMARKERS AND STAGING

- Core needle biopsy (left breast): IDC, grade II, ER 100 %, PR 70 %, Ki67 5 %, Her2 negative
  - Laboratory:
    - **AST 3.06** ukat/l (>5xULN),
    - **ALT 1.24** ukat/l (>2xULN),
    - **AF 11.03** ukat/l (>6xULN),
    - G**GT 30.79** ukat/l (>48xULN),
    - **bilirubin total 75** umol/l (>5xULN),
    - Ca 15-3 >3000 kU/l,
    - LDH 3,52 ukat/l.

voting

QUESTION 1:

FIRST-LINE TREATMENT?

A ENDOCRINE THERAPY

B ENDOCRINE THERAPY + CDK 4/6 INHIBITOR

C CHT

voting

QUESTION 2:

WHAT KIND OF CHT WOULD YOU GIVE?

A TAXANE

B VINORELBINE

C ERIBULIN

D ANTHRACYCLINE

E CAPECITABINE

FIRST-LINE TREATMENT

- March – June 2017 – 12 x weekly vinorelbine 25 mg/m2
- Clinically improvement in PS (now 1), pain well controlled on analgetics, liver border palpable 8 cm above umbilical line
  - Lab Jun 2017:
    - AST 1.33 ukat/l,
    - ALT 1.52 ukat/l,
    - AF 8.46 ukat/l,
    - yGT 33.27 ukat/l,
    - bilirubin total 16 umol/l,
    - Ca 15-3 >3000 kU/l,
    - LDH 3.07 ukat/l.
- CT (thorax, abdomen) Jun 2017: stable disease in liver

voting

QUESTION 3:

AFTER VISCERAL CRISIS IS OVER … WHAT WOULD YOU GIVE NEXT?

A TAMOXIFEN
B TAMOXIFEN + CDK 4/6 INHIBITOR
C TAMOXIFEN + LHRH ANALOG
D AI + LHRH ANALOG
E AI + LHRH ANALOG + CDK 4/6 INHIBITOR
F METRONOMIC CHT

SECOND-LINE THERAPY

- July 2017 – COMPLEEMENT-1:
  - Ribociclib 600 mg
  - Letrozol 2,5 mg
  - Goserelin 3,6 mg
- Patient returned to work, asymptomatic, no analgetics needed, tumour left breast 2 cm, liver border not palpable
- Lab Aug 2018:
  - AST 0.75 ukat/l,
  - ALT 0.96 ukat/l,
  - AF 4.32 ukat/l,
  - yGT 7.16 ukat/l,
  - bilirubin total 5 umol/l,
  - Ca 15-3 344 kU/l,
  - LDH 2.79 ukat/l
- CT Jul 2018: stable liver metastasis (target lesion regression from Oct 2017 22 in 13 mm to 9 and 11 mm in Apr 2018)

voting

QUESTION 4:

WHAT WOULD YOU GIVE AFTER PROGRESSION?

A TAMOXIFEN
B FULVESTRANT
C FULVESTRANT + CDK 4/6 INHIBITOR
D FULVESTRANT + ALPELISIB
E EXEMESTANE + EVEROLIMUS
F CHT

CONCLUSION

- CHT is the optimal choice for the treatment of visceral crisis in luminal subtype of BC
- Otherwise ET (+/- CDK 4/6 inhibitor) is the preferred option in endocrine-responsive BC

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INSTITUTE OF ONCOLOGY
LJUBLJANA

Case 6: Primary metastatic HER2+, HR+ BC

Author: Luka Dobovišek, MD
Mentor: Simona Borštnar, MD, PhD

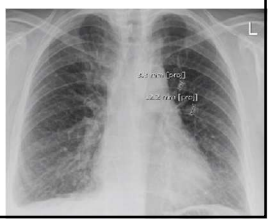
1st Summer School in Medical Oncology
3. - 6. September 2019
LJUBLJANA

CLINICAL PRESENTATION

- 49-year old female, nurse (april, 2019)
- 2 months history of cough
- Skin changes in the right breast (peau d'orange)
- Other medical conditions: none
- Gynecological history: regular menses, 1x partus
- Family history: grandmother on her mother side had BC

CLINICAL PRESENTATION

- Because of the cough hospitalized at the internal medicine department (pneumonia? pulmonary embolism?)
- Abnormal chest x-ray: effusion and pathological lesions
- Pleural puncture: atypical cells – malignant pleural effusion?



voting

QUESTION 1:

WHICH PROCEDURES WOULD YOU ORDER?

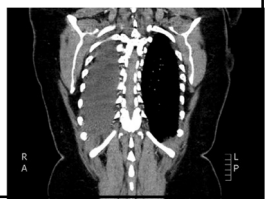
A CT SCAN OF THE ABDOMEN AND THORAX
B BONE SCAN
C CORE NEEDLE BIOPSY (CNB)
D PET-CT
E A + B
F A + B + C

IMAGING STUDIES

- Mammography with tomosynthesis (march, 2019):
  - 23x12 mm tumor formation in the lower two quadrants
  - Thickened skin in the lower quadrants
- Bone scan (april, 2019):
  - Many of the points of increased activity in practically whole axial skeleton – diffuse infiltration

IMAGING STUDIES

- CT (thorax, abdomen, neck):
  - Pronounced thickened skin of right breast
  - Signs of pulmonary lymphangitic carcinomatosis of the right lung with pleural effusion
  - Pericardial effusion
  - Diffuse osteoblastic infiltration of the skeleton



TUMOR BIOMARKERS AND STAGING

- PATHOLOGY:
- Core needle biopsy (17.4.2019):
- IDC, Grade 2, ER 100%, PR 15%, Ki67 25%, HER2+ (IHK 3+)

- LABORATORY:
  - Ca 15-3: 527
  - AF: 2.40
  - AST: 0.79
  - GGT: 0.65

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QUESTION 1:

FIRST-LINE THERAPY?

A CHT + ANTI-HER2 THERAPY
B ET + ANTI-HER2 THERAPY
C CHT
D ET

voting

QUESTION 2:

WHICH CHT WOULD YOU CHOOSE?

A TAXANE
B DOXORUBICIN + CYCLOPHOSPHAMIDE (AC)
C GEMCITABINE + CISPLATIN
D CMF

voting

QUESTION 3:

WHAT KIND OF ANTI-HER2 THERAPY?

A TRASTUZUMAB
B TRASTUZUMAB + PERTUZUMAB
C NERATINIB
D TRASTUZUMAB EMTANSINE (T-DM1)

FIRST-LINE TREATMENT

- Docetaxel + Trastuzumab + Pertuzumab
  - No major AE
  - Taxane induced paronychia, nail changes, fatigue
- Normalization of the tumor marker

voting

QUESTION 4:

HOW LONG DO YOU CONTINUE CHT?

A 2 MONTHS
B 4 MONTHS
C 6 MONTHS
D UNTIL BEST RESPONSE
E UNTIL MAJOR ADVERSE EVENTS

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QUESTION 5:

WHAT KIND OF TREATMENT WOULD YOU GIVE AFTER COMPLETION OF CHT?

A TRASTUZUMAB + PERTUZUMAB
B TRASTUZUMAB + PERTUZUMAB + ET
C TRASTUZUMAB + ET
D ET

voting

QUESTION 6:

WHAT KIND OF ENDOCRINE THERAPY WOULD YOU GIVE?

A AROMATASE INHIBITOR
B TAMOXIFEN
C AROMATASE INHIBITOR + LHRH ANALOG
D TAMOXIFEN + LHRH ANALOG

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QUESTION 7:

WHAT IS EXPECTED MEDIAN OVERALL SURVIVAL FOR THIS PATIENT?

A 12 MONTHS
B 24 MONTHS
C 59 MONTHS

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QUESTION 8:

WHAT THERAPY WOULD YOU GIVE AFTER PROGRESSION?

A CHT
B TRASTUZUMAB EMTANSINE (T-DM1)
C CHANGE THE ENDOCRINE THERAPY AND CONTINUE TRASTUZUMAB + PERTUZUMAB
D NERATINIB

CONCLUSION

- There are many therapeutical options in „triple positive“ (ER+, PR+, HER2+) metastatic BC
- Anti-HER2 therapy is the backbone of HER2+ BC treatment
- Majority of patients with HER2+ disease have long OS

ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY
LJUBLJANA

Case 7: Metastatic TNBC

Author: Luka Dobovišek, MD
Mentor: Simona Borštnar, MD, PhD

1st Summer School in Medical Oncology
3. - 6. September 2019
LJUBLJANA

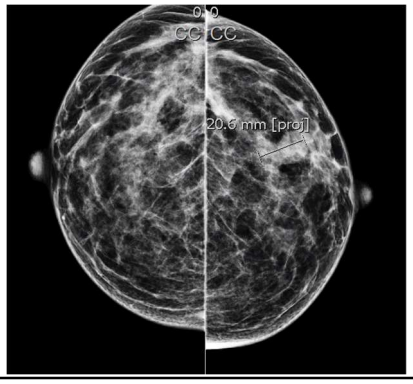
CLINICAL PRESENTATION

- 38-year old female (january, 2017)
- Lump in left breast
- Other medical conditions: none
- Gynecological history: regular menses, 2x partus, uses contraceptive pills
- Family history: aunt had a BC at similar age

IMAGING

- Mammography: 21 mm tumor formation in upper outer quadrant of the left breast
- US guided core needle biopsy with clip marking
- US of left axilla: one pathological lymph node
  - FNA: adenocarcinoma
- CT (thorax, abdomen): tumor formation in left breast, 3 pathological ipsilateral internal mammary nodes

MAMMOGRAPHY



TUMOR BIOMARKERS AND STAGING

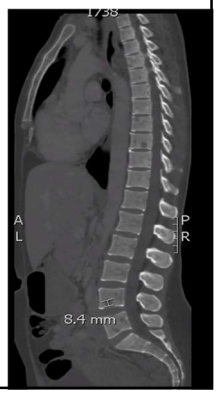
- Core needle biopsy:
  - IDC
  - Grade 3
  - ER 0%
  - PR 0%
  - HER-2 neg.
  - Ki67 50%
- Germline BRCA 1/2 negative

NACT AND OPERATION

- 4x dd AC + 4x dd paclitaxel with growth factor support
- CT (thorax): partial response in the left breast, complete response in internal mammary nodes (may, 2017)
- Breast conserving surgery with SLNB and ALND (june, 2017)
- Pathological examination after NACT:
  - Partial response in the breast: 9 mm residual tumor
  - 1/27 positive nodes: 5 mm, focal extracapsular extension, lymphovascular invasion

ADJUVANT CHT AND RT

- RT (august - september, 2017)
  - 50 Gy in 28 fractions
- Capecitabine 8 cycles (september, 2017 - february, 2018)
- Lower back and hip pain (april, 2018)
- CT (thorax, abdomen):
  - pathological lymph nodes in mediastinum,
  - new lytic bone lesions (spine, ribs, right sacrum)



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QUESTION 1:

FIRST-LINE THERAPY FOR mTNBC BC?

A GEMCITABINE - CISPLATIN
B VINORELBINE
C ERIBULIN
D CAPECITABINE
E TAXANE + IMMUNOTHERAPY (ATEZOLIZUMAB)
F PALLIATIVE RADIATION THERAPY

METASTATIC DISEASE

- Palliative radiation to the sacroiliacal joint (12 Gy) and 10th rib (9 Gy)
- Gemcitabine-cisplatin /3 week (june - september, 2018)
  - AE: fatigue, neutropenia (+ pegfilgrastim)
- CT (thorax, abdomen): regression of nodal and skeletal metastases (september, 2018)
- After 4 cycles refuses further therapy

voting

QUESTION 2:

WHAT WOULD YOU DO NOW?

A ERIBULIN
B VINORELBINE
C CAPECITABINE
D METRONOMIC CM
E WAIT UNTIL PROGRESSION

METASTATIC DISEASE

- NGS (Foundation One):
  - somatic mutation of BRCA1
  - FGFR2 amplification, TP53 mutation
  - MS-Stable
  - TMB-low (4 muts/Mb)
- Olaparib (PARPi) 2x 300 mg (november, 2018)
  - AE: nausea, diarrhea, loss of appetite, fatigue, depression
- She refuses further therapy after 2 weeks

DISEASE PROGRESSION

- Pain in thoracic spine (january, 2019)
  - CT (thorax, abdomen): progression of skeletal metastasis and pathological fracture of TH9 and L2.
- Confusion and headache (february, 2019)
  - CT (head): diffuse metastatic infiltration of the brain, intrametastatic hemorrhage, herniation in foramen ovale

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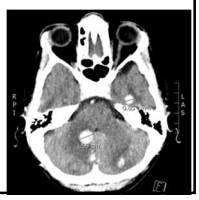
QUESTION 3:

TREATMENT FOR CNS METASTASIS?

A RADIOTHERAPY
B SYSTEMIC THERAPY
C RADIOTHERAPY FOLLOWED BY SYSTEMIC THERAPY

PROGRESSION IN THE CNS

- RADIOTHERAPY:
  - Palliative radiation to the head (30 Gy)
  - Palliative radiation to the spine Th9-L2 (20 Gy)
- Hospitalized for symptomatic treatment and dies at the department (march, 2019)



CONCLUSION

- mTNBC is the subtype with the worst prognosis with mOS approximately 1 year
- TNBC remains a challenge in everyday clinical practice, new therapies are in active development
- New therapies are needed for CNS metastasis in all BC types

1st Summer School in Medical Oncology –
Standards and Open Questions

Systemic treatment in advanced soft tissue sarcoma (STS): what is standard, what is new

Mojca Unk, MD, MSc
Institute of Oncology Ljubljana
Department of Medical Oncology

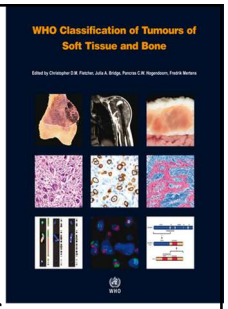
3. - 6. September 2019

Audience….

1st question

- How confident are you in systemic treatment of advanced STS?
- 1. very confident
- 2. somehow confident
- 3. not confident at all

Background



- Heterogeneous group of rare neoplasms with mesenchymal origin
- More than 70 different entities
- Strong tendency toward local recurrence (10 -30 %) and metastatic spreading (30 – 40 %)
- Lung: most common site of STS metastases
- Pulmonary metastasectomy - the standard treatment for selected patients with limited lung disease
- Chemotherapy - the most relevant role in the management of metastatic disease
- Outcome for M1 disease - very poor (mOS 14–17 months)

Fletcher et al.IARC 2013;Judson et al.Lancet Oncol. 2014; Ryan et al. JCO 2016; Tap et al. Lancet. 2016.

Prognostic factors

- Age (> 60 y)
- Size (> 5 cm)
- Grade (high)
- Mitotic count (high)
- Location (limb or torzo)
- Deep
- Lymph nodes positive

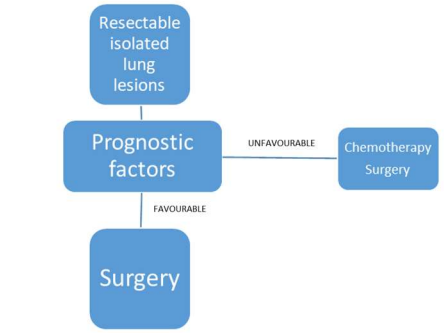
- Lung; most common site
  - liver; visceral STS
- Complex treatment (multidisciplinary decision); mostly systemic
- Poor prognosis: mOS 14 m

Pisters et al. JCO, 1996; Singer et al. Ann Surg, 1994; Van Glabbeke et al. JCO, 1999; Gustafson et al. Acta Orthop Scand, 1994; Lewis et al. Ann Surg, 1998; Trovik et al. Eur J Cancer, 2000; Erten et al. J Surg Oncol, 2005. ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann Oncol 2018

Pulmonary resection

surgery of isolated lung metastases

5-y OS 32 %



Blackmon et al. Ann Thorac Surg 2009

J Thorac Cardiovasc Surg. 1984 Feb;87(2):260-8.

Analysis of prognostic factors in patients undergoing resection of pulmonary metastases from soft tissue sarcomas.

Putnam JB Jr, Roth JA, Wesley MN, Johnston MR, Rosenberg SA.

- the tumour doubling time (20 days; mOS 22 vs 6 m)
- the number of metastases on preoperative CT (4 mets; mOS 23 vs 6 m)
- the disease-free interval (12 m; mOS 32 vs 10 m)

STS – 1st line systemic treatment

Lancet Oncol 2014; 15: 415–23

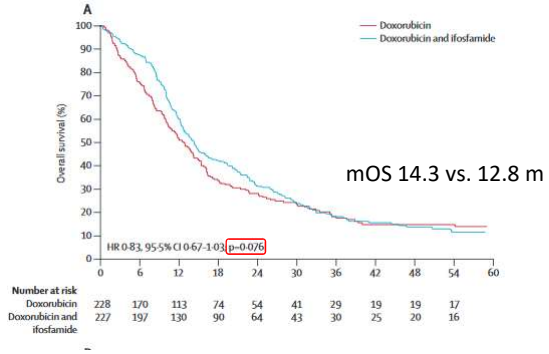
Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial

*Ian Judson, Jaap Verweij, Hans Gelderblom, Jörg T Hartmann, Patrick Schöffski, Jean-Yves Blay, J Martijn Kerst, Josef Sufliarsky, Jeremy Whelan, Peter Hohenberger, Anders Krarup-Hansen, Thierry Alcindor, Sandrine Marreaud, Saskia Litière, Catherine Hermans, Cyril Fisher, Pancras C W Hogendoorn, A Paolo dei Tos, Winette T A van der Graaf, for the European Organisation and Treatment of Cancer Soft Tissue and Bone Sarcoma Group**

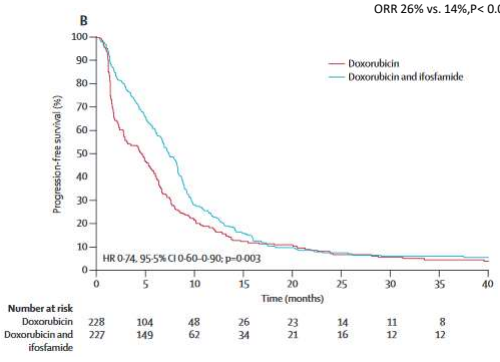
	Doxorubicin group (n=228)	Doxorubicin and ifosfamide group (n=227)
Complete response	1 (<1%)	4 (2%)
Partial response	30 (13%)	56 (25%)
Stable disease	105 (46%)	114 (50%)
Progressive disease	74 (32%)	30 (13%)
Early death (progression)	4 (2%)	5 (2%)
Early death (other cause)	3 (1%)	2 (1%)
Not evaluable	11 (5%)	16 (7%)

Data are n (%).

ORR 26% vs. 14%,P< 0.0006



mOS 14.3 vs. 12.8 m



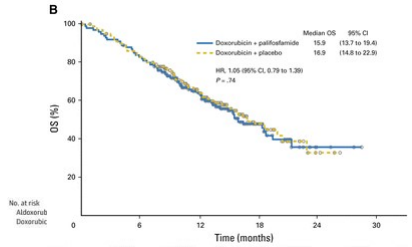
Mono/polychemotherapy

author	chemotherapy	Pt (number)	response rate	survival
Muss (1985)	A/AC	104	NS	NS
Omura (1983)	A/AD	146	NS	NS
Borden (1987)	A/AD	186	**AD 30% (p=.02)**	NS
Lerner (1987)	A/AD	66	**AD 40% (LMS)**	NS
Santoro (1995)	A/AI/CYVADIC	449	NS	NS
Borden (1990)	A/AV	195	NS	NS
Edmonson (1993)	A/AI/APM	262	**AI 34%** (p=.03)	NS
Antman (1993)	AD/MAID	340	**MAID 32 %** (p=.02)	NS
Judson (2014)	A/AI	415	**AI 26%** (A 14%)	NS
Ryan (2013)	A/APal	447	**APal 28%** (A 19%)	NS

NO SURVIVAL BENEFIT; doxorubicin 75mg/m² is golden standard for more than 40 years!

A- doxorubicin; C- cyclofosfamid; D-dacarabazin; I- ifosfamid; CYVADIC- cyclofosfamid, vincristin, doxorubicin, dacarabazin; MAID- mesna, doxorubicin, ifosfamid, dacarabazin; V-vincristin; APM-doxorubicin, cisplatin, mitomycin; Pal-palifosfamid

…. no convincing evidence of superiority as upfront treatment (prodrugs, novel drugs)



- Amrubicin (3rd gen)
  - nonrandomised single arm phase II: similar results as dox
  - cardiac sparing alternative
- Aldoxorubicin (prodrug of doxorubicin) with a pH-sensitive linker; activity in acidic tumour environment: enhancing activity and minimising toxicity

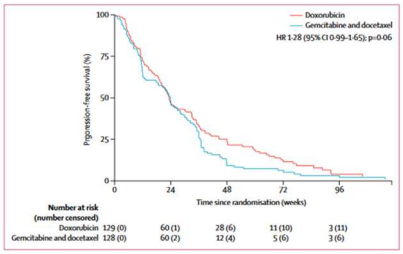
  phase 2b: aldoxo vs doxo ↑ PFS (5.6 vs. 2.7 months;P= 0.02) ↑ORR (25% vs. 0%)

  on-going phase Ib: safety and activity of aldoxo + ifo
- Palifosfamide (active metabolite of ifosfamide)
  - Neg PICASSO III (palif+doxo vs doxo)

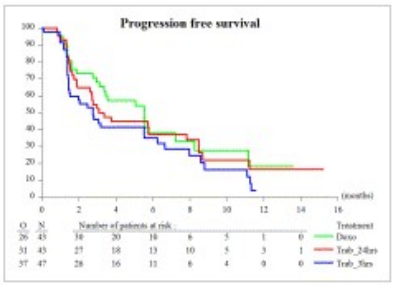
Gupta et al. Invest New Drugs 2016; Chawla et al. JAMA Oncol.2015; Verschraegen et al. JCO 2010

…. no convincing evidence of superiority as upfront treatment (the upfront administration of compounds known to be active in further lines)

- GeDDiS: gem+doce vs doxo
  - no differential treatment effect by histological subtype (p=0·24)
  - superiority of single agent doxo: ORR (65.9% vs. 58.6%)
  - PFS(23 vs. 24 weeks)



- Trabectidin: 2 phase 2 trails
  - Trabectidin (3 or 24h inf.) vs doxo; neg
  - Trabectidin + doxo vs doxo; stopped for futility



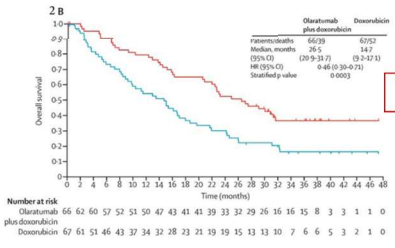
Seddon et al. Lancer Oncol 2014. Bui-Nguyen et al. Eur JCancer 2015;Martin-Broto et al. JCO 2016.

…. no convincing evidence of superiority as upfront treatment (monoclonal antibodies)

ANNOUNCE: A randomized, placebo (PBO)-controlled, double-blind, phase (Ph) III trial of doxorubicin (dox) + olaratumab versus dox + PBO in patients (pts) with advanced soft tissue sarcomas (STS).

Tap et al. ASCO 2019.

ANNOUNCE did not confirm that olaratumab + doxorubicin, followed by olaratumab monotherapy, improves OS over doxorubicin in pts with advanced STS. Further analyses are warranted to explore the inconsistent outcomes between the Ph 3 and Ph 2 studies.



+ 12months!

Lancet. 2016 July 30; 388(10043): 488–497. doi:10.1016/S0140-6736(16)30587-6.

Olaratumab and doxorubicin versus doxorubicin alone in soft tissue sarcoma

William D. Tap, MD[1], Robin L. Jones, MD[2,a], Brian A. Van Tine, MD[3], Bartosz Chmielowski, MD[4], Anthony D. Elias, MD[5], Douglas Adkins, MD[3], Mark Agulnik, MD[6], Matthew M. Cooney, MD[7], Michael B. Livingston, MD[8], Gregory Pennock, MD[9], Meera R. Hameed, MD[10], Gaurav D. Shah, MD[11], Amy Qin, PhD[12], Ashwin Shahir, MD[13], Damien M. Cronier, PhD[13], Robert Ilaria Jr, MD[14], Ilaria Conti, MD[14], Jan Cosaert, MD[12,b], and Gary K. Schwartz, MD[15]

Targeted therapy

- Dermatofibrosarcoma protuberans (DFSP) and imatinib
  translocation COL1A1/PDGFB fusion gene → PDGFRB activation
  metastatic potencial- fibrosarcomatous (FS) component
  imatinib mesylate: ORR 60–70%
  FS-DFSP: translocation +, imatinib sensitivity + with RR ~ 80%, but shorter duration

- Alveolar soft part sarcoma (ASPS)
  - Chemo resistant, MET overexpression
  - Antiangigenetic drugs: sunitinib, pazopanib, cediranib
  - MET inhibitors: crizotinib
  - Immunotherapy (phase 2: atezo and tremi/durva)

- Solitary fibrous tumour (SFT)
  - NAB2-STAT6 fusion
  - Chemotherapy but also antiangiogenetic drugs: sunitinib, sorafenib, pazopanib, axitinib

Simon et al.Nat Genet 1997;Greco et al.Oncogene 1998;Stacchiotti et al.Clin Can Res 2016; Reichardt et al. EJC 2003; Stacchiotti et al. EJC 2013;Somaia , discussant@CTOS2018; Schoffski et al, Ann Oncol 2017; Judson et al, Lancet Oncol2019.

Doxorubicin remains the standard of care, with or without ifosfamide!

STS – further line systemic treatment

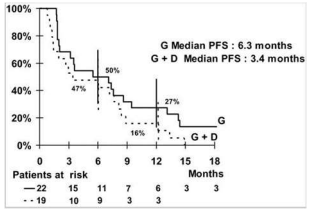
Further lines

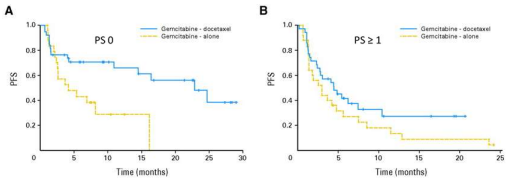
- Histology driven treatment:
  - Chemotherapy
  - TKI targeting angiogenesis
  - Other TKI
  - Immunotherapy
- Best supportive care

Chemotherapy

Gemcitabine (alone or in combintion)

- LMS: gem+doce; conflicting results



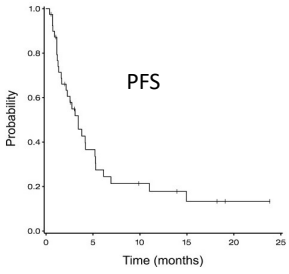


Pautier et al. Oncologist 2012; Maki et al, JCO 2007

- Gem+vinorelbin

clinical benefit rate 25%

Dileo et al, cancer 2008



- Gem+dacarbazine

mPFS 4.2 vs. 2 m, P = 0.005

mOS 16.8 vs. 8.2 m, P = 0.014

clinical benefit rate (49% vs. 25%, P = 0.009

Garcia del Muro et al, JCO 2011

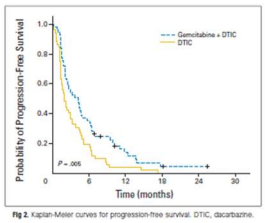


Fig 2. Kaplan-Meier curves for progression-free survival. DTIC, dacarbazine.

VOLUME 34 · NUMBER 8 · MARCH 10, 2016

JOURNAL OF CLINICAL ONCOLOGY

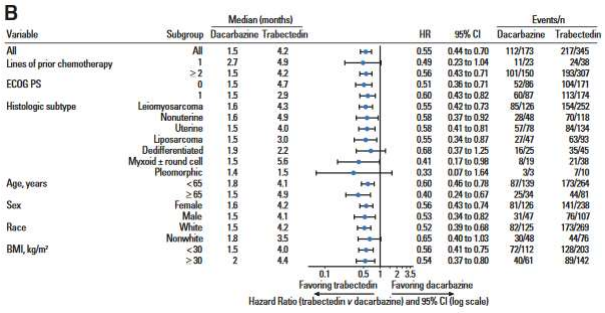
ORIGINAL REPORT

Efficacy and Safety of Trabectedin or Dacarbazine for Metastatic Liposarcoma or Leiomyosarcoma After Failure of Conventional Chemotherapy: Results of a Phase III Randomized Multicenter Clinical Trial

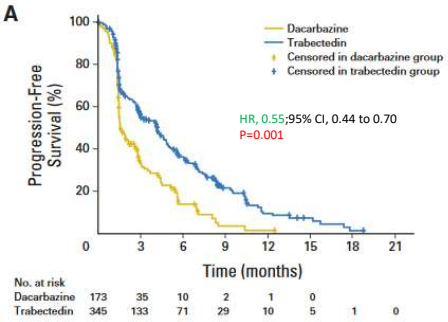
George D. Demetri, Margaret von Mehren, Robin L. Jones, Martee L. Hensley, Scott M. Schuetze, Arthur Staddon, Mohammed Milhem, Anthony Elias, Kristen Ganjoo, Hussein Tawbi, Brian A. Van Tine, Alexander Spira, Andrew Dean, Nushmia Z. Khokhar, Youn Choi Park, Roland F. Knoblauch, Trilok V. Parekh, Robert G. Maki, and Shreyaskumar R. Patel

myxoid liposarcoma: t(12;16)(q13;p11)
additional 'targeted' mechanism of action
Inactivation FUS-CHOP oncogene

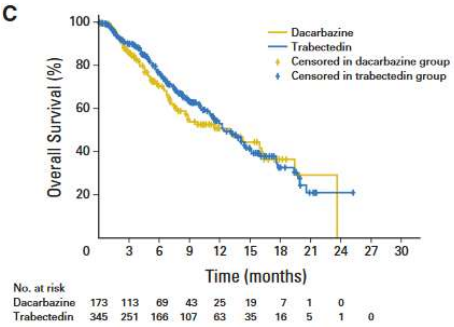
B



A



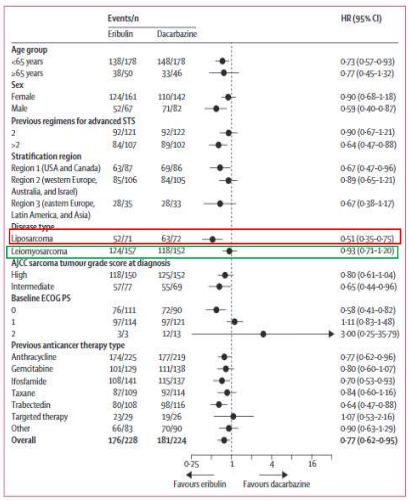
C



Lancet 2016; 387: 1629–37

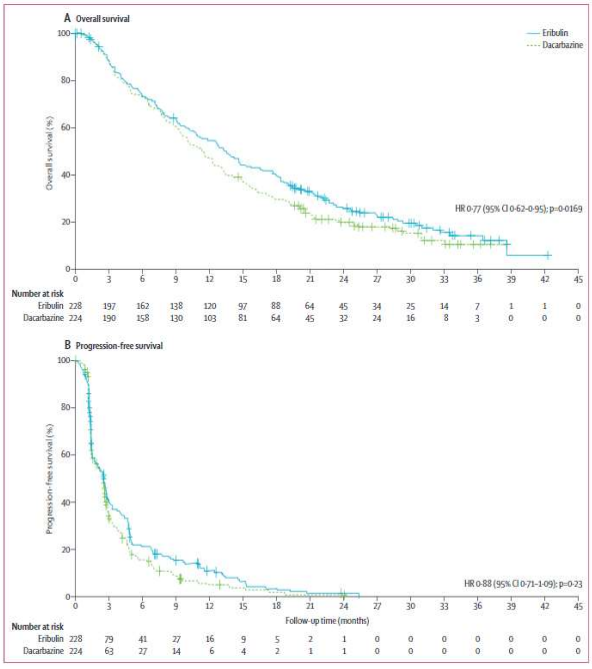
Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial

Patrick Schöffski, Sant Chawla, Robert G Maki, Antoine Italiano, Hans Gelderblom, Edwin Choy, Giovanni Grignani, Veridiana Camargo, Sebastian Bauer, Sun Young Rha, Jean-Yves Blay, Peter Hohenberger, David D'Adamo, Matthew Guo, Bartosz Chmielowski, Axel Le Cesne, George D Demetri, Shreyaskumar R Patel



	Eribulin (n=228)	Dacarbazine* (n=224)
Disease type		
Liposarcoma	75 (33%)	78 (35%)
Leiomyosarcoma	152 (67%)	145 (65%)
Other	1 (<1%)	1 (<1%)

LPS: mOS 15·6 vs 8·4 m
LMS: mOS 12·7 vs 13·0 m



VOLUME 26 · NUMBER 32 · NOVEMBER 10 2008

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase II Trial of Weekly Paclitaxel for Unresectable Angiosarcoma: The ANGIOTAX Study

Nicolas Penel, Binh Nguyen Bui, Jacques-Olivier Bay, Didier Cupissol, Isabelle Ray-Coquard, Sophie Piperno-Neumann, Pierre Kerbrat, Charles Fournier, Sophie Taieb, Marta Jimenez, Nicolas Isambert, Frédéric Peyrade, Christine Chevreau, Emmanuelle Bompas, Etienne G.C. Brain, and Jean-Yves Blay

From the Département de Cancérologie Générale, Unité de Biostatistiques, and

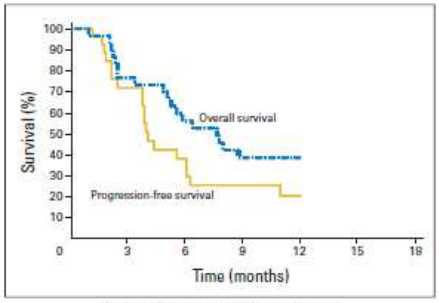


Fig 1. Overall and progression-free survival.

Table 3. Response Rates

Disease Status	No. of Patients		
	At 2 Months	At 4 Months	At 6 Months
Assessable patients	27*	22	21
Progressive disease	7	12	16
Complete response	0	1	3†
Partial response	5	3	1
Stable disease	15	6	1
Overall response rate			
%	18	18	19
95% CI	4 to 33	2 to 34	3 to 35
Nonprogression rate			
%	74	45	24
95% CI	57 to 90	25 to 66	6 to 42

*Three patients of the 30 enrolled patients were not assessable because of the following reasons: death by unrelated stroke (one patient), severe toxicities with treatment cessation (two patients).
†Complete responses were obtained by surgery (Table 4).

weekly paclitaxel seems to be an effective and well-tolerated treatment for patients with unresectable angiosarcoma

Histology driven approach

Histology	Cytotoxic compounds with selective activity
Leiomyosarcoma	Gemcitabine ± docetaxel, trabectedin, dacarbazine
Dedifferentiated liposarcoma	High-dose ifosfamide, trabectedin, eribulin
Myxoid liposarcoma	Trabectedin, eribulin
Synovial sarcoma	Ifosfamide, trabectedin
Epithelioid sarcoma	Gemcitabine
Angiosarcoma/intimal sarcoma	Gemcitabine, paclitaxel
Alveolar soft part sarcoma	
Solitary fibrous tumour	Dacarbazine
Clear cell sarcoma	
Extraskeletal myxoid chondrosarcoma	
Perivascular epithelioid cell tumor	Gemcitabine
Epithelioid hemangioendothelioma	
Inflammatory myofibroblastic tumour	
Undifferentiated pleomorphic sarcoma	High-dose ifosfamide, gemcitabine
Dermatofibrosarcoma protuberans	

Frezza et al. BMC Medicine 2017

TKI targeting angiogenesis

Lancet 2012; 379: 1879–86

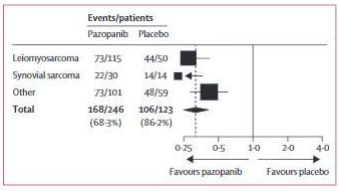
Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial

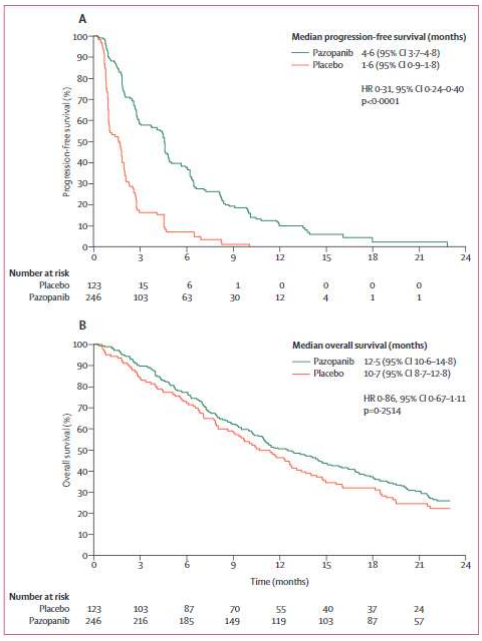
Winette T A van der Graaf, Jean-Yves Blay, Sant P Chawla, Dong-Wan Kim, Binh Bui-Nguyen, Paolo G Casali, Patrick Schöffski, Massimo Aglietta, Arthur P Staddon, Yasuo Beppu, Axel Le Cesne, Hans Gelderblom, Ian R Judson, Nobuhito Araki, Monia Ouali, Sandrine Marreaud, Rachel Hodge, Mohammed R Dewji, Corneel Coens, George D Demetri, Christopher D Fletcher, Angelo Paolo Dei Tos, Peter Hohenberger, on behalf of the EORTC Soft Tissue and Bone Sarcoma Group and the PALETTE study group

Excluded:

adipocytic sarcoma

embryonal rhabdomyosarcoma
bone sarcoma
PNET
GIST
dermatofibrosarcoma protuberans
inflammatory myofibroblastic sarcoma





Other TKI, targeting angiogenesis

- Sorafenib
- Regorafenib
- Sunitinib
- Cediranib
- Tivozantinib

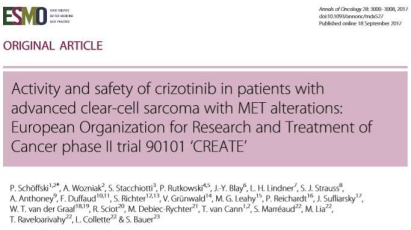
Ray-Coquard et al, Oncologist. 2012; Mir et al, Lancet Oncol. 2016;Hindi et al, JCO 2015; Kummar et al, JCO 2013; Agulnik et al, Ann Oncol 2017

Other TKI

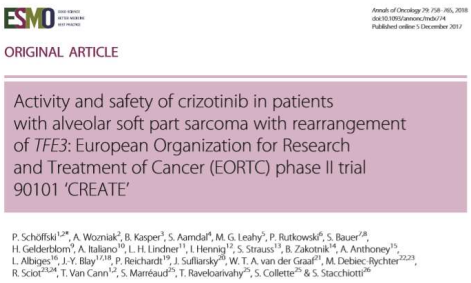
- crizotinib

THE LANCET
Respiratory Medicine

crizotinib for pts with locally advanced or metastatic ALK-positive IMFT



crizotinib provided clinical benefit to patients with locally advanced or metastatic MET+ CCSA



crizotinib has activity in TFE3 rearranged ASPS MET+ pts

Immunotherapy

Immunotherapy in STS

Study	Population	Study phase, status	Drug and schedule	Patients	Overall response rate (%)
Mackall et al., 2016 [88]	Synovial sarcoma	I/II, recruiting	NY-ESO-1c259 SPEAR T-cells Cohort 1 and 2: FL 30 mg/m^2/day, day 1–4; CTX 1800 mg/m^2/day day 1–2 Cohort 3: CTX 1800 mg/m^2/day day 1–2 Cohort 4: FL 30 mg/m^2/day, day 1–3; CTX 600 mg/m^2/day; day 1–3	Cohort 1: 15 Cohort 2: 2 Cohort 3: 2 Cohort 4: 0	Cohort 1: 50 Cohort 2: NA Cohort 3: NA Cohort 4: NA
Italiano et al., 2016 [90]	LMS (Arm A), UPS (Arm B), GIST (Arm C), OS (Arm D), other sarcomas (Arm E)	II, recruiting in arm B and D	Pembrolizumab 200 mg i.v. 3-weekly; CTX 50 mg BID 1week on, 1 week off	Arm A: 15 Arm B: 0 Arm C: 10 Arm D: 0 Arm E: 16	No objective responses
Burgess et al., 2016 [89]	All-type STS (arm A) and BS (arm B)	II, completed	Pembrolizumab, 200mg i.v., 3-weekly	Arm A: 40 Arm B: 40	Arm A: 17.5 (UPS, LPS, SS) Arm B: 5 (OS, CS)
Paoluzzi et al., 2016 [91]	All-type STS and BS	Retrospective	Arm A: nivolumab 3 mg/kg i.v., 2-weekly Arm B: nivolumab 3 mg/kg i.v., 2-weekly + pazopanib 800 mg/day	Arm A: 10 Arm B: 18	Arm A: 10 (CS) Arm B: 11 (ES, OS)
George et al., 2016 [90]	Leiomyosarcoma	II	Nivolumab 3 mg/kg i.v., 2-weekly	12	No objective responses

BS bone sarcomas; *CS* chondrosarcoma; *CTX* cyclophosphamide; *ES* epithelioid sarcoma; *FL* fludarabine; *GIST* Gastrointestinal stromal tumors; *LMS* leiomyosarcoma; *LPS* liposarcoma; *NA* not available; *OS* osteosarcoma; *SS* synovial sarcoma; *STS* soft tissue sarcomas; *UPS* undifferentiated pleomorphic sarcoma

Frezza et al. BMC Medicine 2017

Conclusion

- Doxorubicin remains the standard in the treatment of advanced STS
- Combination with ifosfamide: fit patients, tumour response needed, histologies with selective sensitivity to alkylating agents
- Beyond the 1st line: histology driven treatment
- Newer strategies (drugs targeting epigenetic mechanisms and immunotherapies) are being developed to improve the outcome in this population.

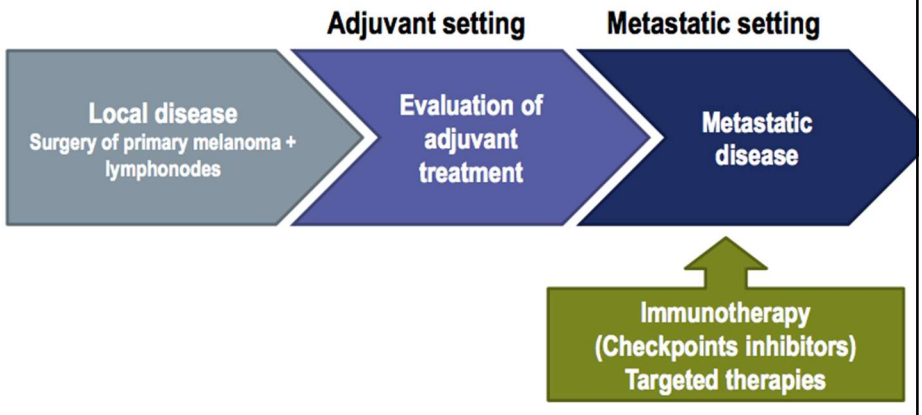
Thank you for your attention!

1st Summer School in medical oncology - Standards and open questions
Ljubljana 2019

Adjuvant treatment strategies for malignant melanoma

Davorin Herceg
University Hospital Zagreb

MELANOMA PATIENT HISTORY: RESEARCH AREAS



Drugs used in metastatic setting have been experimented in the adjuvant setting

ADJUVANT TREATMENTS IN MELANOMA

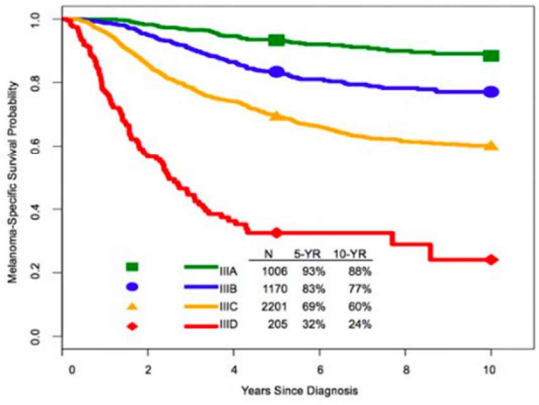
Agenda

- Risk category
- 90s – 2016: Interferon
- 2016: Ipilimumab
- 2017: New treatments
  - Immunotherapy: AntiPD1
    - Nivolumab
    - Pembrolizumab
  - Targeted therapies:
    - Vemurafenib
    - Dabrafenib + trametinib

MSS according to Stage III Groups

8th Edition international melanoma database

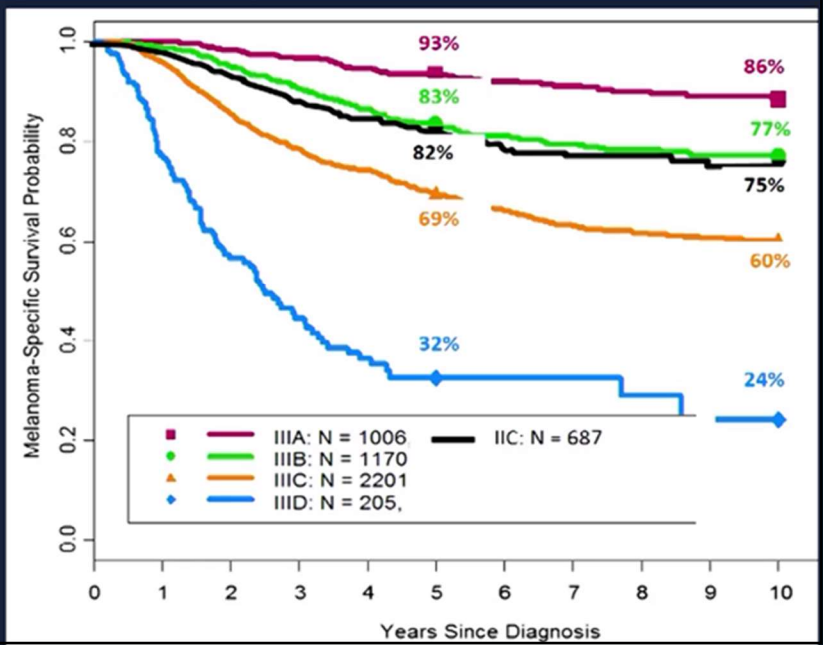
- Stage group stratification based on both T- and N-category criteria
  - Tumor thickness
  - Ulceration
  - # LNs
  - Microsatellite/ITM/satellites
- Recursive partitioning → final = 4 stage groups
- Significant heterogeneity



Gershenwald, Scolyer, Hess, Sondak et al. CA Cancer J Clin. 2017 Oct 13. doi: 10.3322/caac.21409. [Epub ahead of print]

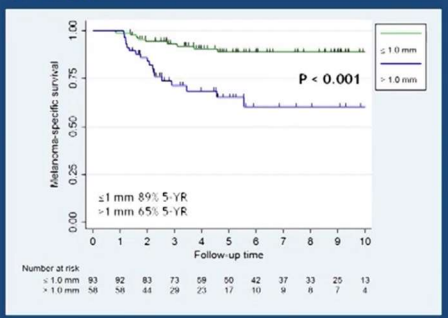
AJCC 2018: Stage III Survival

Willekind 2017, TNM handbook 2017

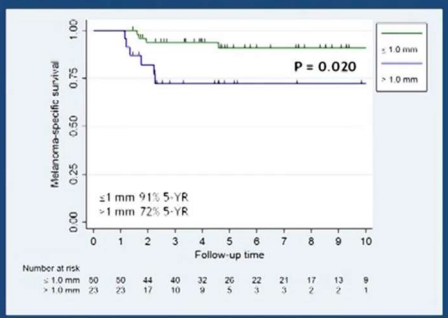


Survival differentiation in stage IIIA

7th edition



8th edition

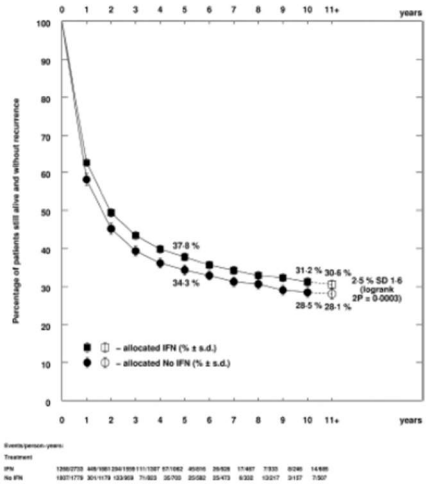


Schedule	Dose	Frequency	Duration
Low dose			
	3 miu	3 x weekly	18-24 months
Intermediate dose			
Induction	10 miu	5 x weekly	4 weeks
Maintenance	10 miu	3 x weekly	12-24 months
	5 miu	3 x weekly	24 months
High dose			
Induction	20 MIU/m^2	5 x weekly	4 weeks
Maintenance	10 MIU/m^2	3 x weekly	11 months
Short course			
Induction x 1	20 MIU/m^2	5 x weekly	4 weeks
Intermittent			
Induction x 3	20 MIU/m^2	5 x weekly	4 weeks Q4 months

	Overall risk	
Dose	Event Free Survival	Overall Survival
High (N=1196)	0.83 (0.72-0.96)	0.93 (0.80-1.08)
Peg-IFN (N=1256)	0.83 (0.76-1.00)	0.96 (0.82-1.11)
Intermediate (N=2243)	0.84 (0.74-0.95)	0.91 (0.79-1.04)
Low (N=2732)	0.85 (0.77-0.94)	0.86 (0.77-0.96)
Very low (N=484)	0.99 (0.80-1.23)	0.96 (0.76-1.21)

INTERFERON A – META ANALYSIS 2017

Survival curve for event-free survival



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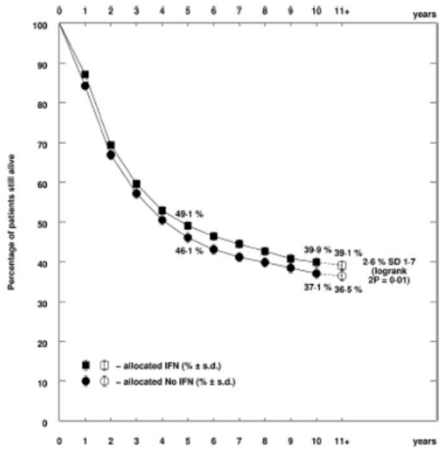
INTERFERON A – META ANALYSIS 2017

Survival curve for Overall Survival



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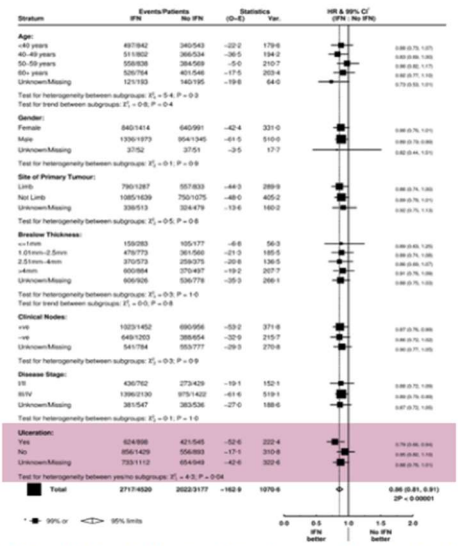
META ANALYSIS 2017

Subgroup analysis for relapse free survival



Reprinted from Eur Cancer, 82, Ives NJ, *et al.* Adjuvant interferon-α for the treatment of high-risk melanoma: An individual patient data meta-analysis; 171-183. Copyright 2017, with permission from Elsevier.

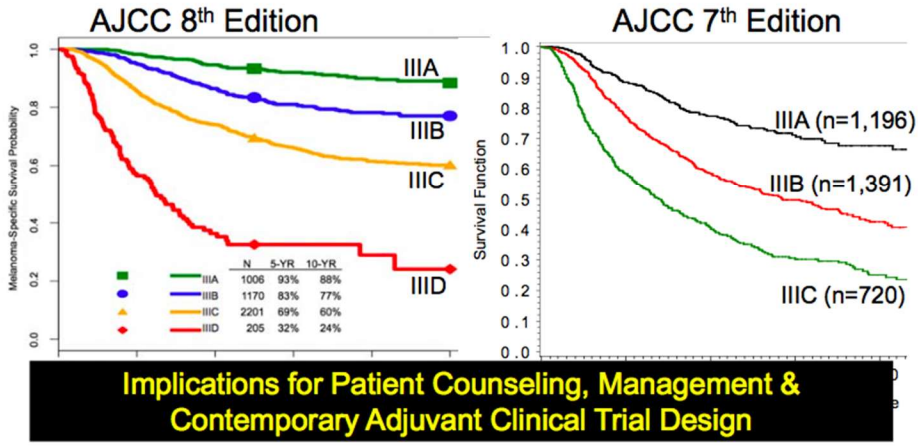
- Modest activity with relatively few adverse events (on low-dose IFN) and serious toxicity (on high-dose IFN)
- In Europe mainly LDI is still used for high-risk AJCC stage IIB/C (SN-negative pts)
- No longer used for stage III patients
- No future for interferons from 2021+!?

Adjuvant Melanoma Trials: Potential Pitfalls

All trials on stage III patients have been conducted

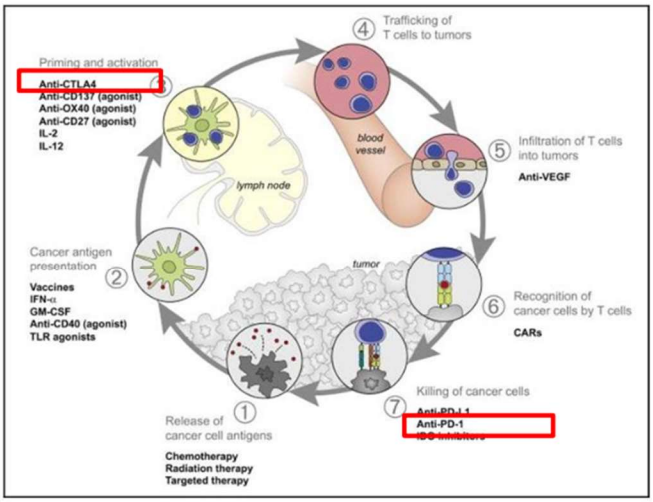
- with selection criteria based on the AJCC 7th edition melanoma classification
- with patients who received a complete lymphadenectomy (CLND)

MSS according to AJCC Stage III Group



Implications for Patient Counseling, Management & Contemporary Adjuvant Clinical Trial Design

Immune checkpoint inhibitors



Reprinted from Immunity 2013; 39(1), Chen DS, Mellman I, Oncology Meets Immunology: The Cancer-Immunity Cycle; 1-10. Copyright 2013, with permission from Elsevier.

CheckMate-238 Study Schema

Randomized, phase 3 study of adjuvant NIVO vs IPI after complete resection of high-risk stage III/IV melanoma

- ≥ 15 year old with melanoma
- Stage IIIb/c or IV before complete resection
- Complete surgical resection
- No prior medical therapy for melanoma treatment
- No ocular/uveal melanoma

RANDOMIZED

1:1

N = 453

NIVO 3 mg/kg + IPI PBO IV
Q2 weeks x 4 doses, then
Q12 weeks starting at week 24

N = 453

IPI 10 mg/kg + NIVO PBO IV
Q2 weeks x 4 doses, then
Q12 weeks starting at week 24

Trial dates: 3/2015 – 11/2019 *(estimated)*

- **Primary endpoint:** RFS (up to 36 months, ITT population).
- **Secondary endpoints:** OS (up to 48 months).

ITT = intention to treat.

NCT02388906. Weber J et al. *N Engl J Med.* 2017;377:1824-1835.

Adjuvant Nivolumab in CheckMate-238: RFS in All Patients

	NIVO	IPI
Events/patients	171/453	221/453
Median (95% CI)	30.8 (30.8, NR)[a]	24.1 (16.6, NR)
HR (95% CI)	0.66 (0.54, 0.81)	
Log-rank *P* value	<0.0001	

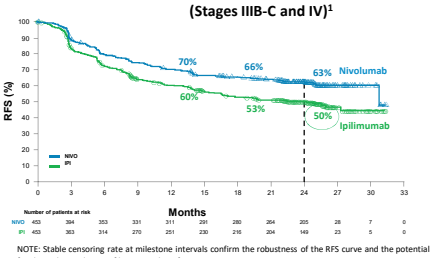
[a]Median estimate not reliable or stable due to few patients at risk.

24-month RFS rates were significantly longer for NIVO vs IPI, with DMFS also remaining significantly longer for NIVO (70.5%) vs IPI (63.7%).

Weber J, et al ASCO 2018.

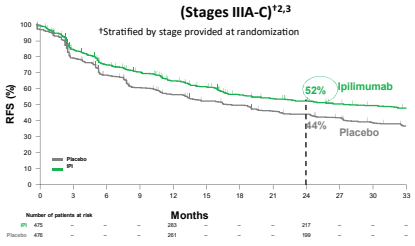
Nivolumab demonstrated superior RFS benefit vs. ipilimumab, an active comparator with proven 5-year OS benefit

CA209-238 Kaplan-Meier plot of RFS (Stages IIIB-C and IV)[1]



CA184-029 Kaplan-Meier plot of RFS (Stages IIIA-C)[†2,3]

†Stratified by stage provided at randomization



NOTE: Stable censoring rate at milestone intervals confirm the robustness of the RFS curve and the potential for this to be predictive of long-term benefit

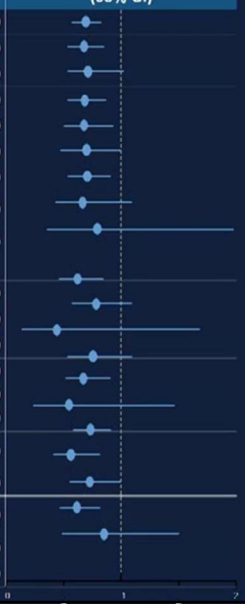
	Nivolumab	Ipilimumab
Events/patients	171/453	221/453
Median (95% CI)	30.8 (30.8, NR)	24.1 (16.6, NR)
HR (95% CI), *P* value	0.66 (0.54, 0.81), <0.0001	

	Ipilimumab	Placebo
Events/patients	264/475	323/476
Median (95% CI)	27.6 (19.3, 37.2)	17.1 (13.6, 21.6)
HR (95% CI), *P* value	0.76 (0.64, 0.89), 0.0008	

- Significantly fewer patients experienced relapse or death with nivolumab than with active control, ipilimumab[1]
- Nivolumab magnitude of benefit is durable through 2 years[1]
- Informal comparison of CA209-238 and CA184-029 results suggests that nivolumab RFS rates are even greater than placebo[1,2]

RFS: Pre-specified Subgroups

Subgroup		No. of events/no. of patients		Unstratified HR (95% CI)	Unstratified HR (95% CI)
		NIVO 3 mg/kg	IPI 10 mg/kg		
Overall	Overall	171/453	221/453	0.68 (0.56, 0.83)	
Age	<65 years	117/333	158/339	0.67 (0.53, 0.85)	
	≥65 years	54/120	63/114	0.70 (0.49, 1.01)	
Sex	Male	106/258	141/269	0.69 (0.53, 0.88)	
	Female	65/195	80/184	0.68 (0.49, 0.94)	
Stage (CRF)	Stage IIIb	48/165	60/148	0.68 (0.47, 1.00)	
	Stage IIIc	87/203	114/218	0.68 (0.52, 0.91)	
	Stage IV M1a-M1b	27/62	37/66	0.66 (0.40, 1.08)	
	Stage IV M1c	8/20	10/21	0.78 (0.31, 1.99)	
	Not reported	1/1	0/0		
Stage III: Ulceration	Absent	64/201	100/216	0.61 (0.44, 0.83)	
	Present	68/154	68/135	0.77 (0.55, 1.08)	
	Not reported	3/15	6/15	0.42 (0.11, 1.70)	
Stage III: Lymph node involvement	Microscopic	46/126	59/134	0.75 (0.51, 1.10)	
	Macroscopic	82/219	107/214	0.66 (0.49, 0.88)	
	Not reported	7/25	8/18	0.53 (0.19, 1.48)	
PD-L1 status	<5%/indeterminate	132/300	157/299	0.73 (0.58, 0.91)	
	≥5%	39/152	64/154	0.54 (0.36, 0.81)	
***BRAF* mutation status**	Mutant	73/187	95/194	0.73 (0.54, 0.99)	
	Wild-type	73/197	107/212	0.61 (0.45, 0.82)	
	Not reported	25/69	19/47	0.85 (0.47, 1.55)	



AE, n (%)	NIVO (n = 452)		IPI (n = 453)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any AE	438 (97)	115 (25)	446 (98)	250 (55)
Treatment-related AE	385 (85)	65 (14)	434 (96)	208 (46)
Any AE leading to discontinuation	44 (10)	21 (5)	193 (43)	140 (31)
Treatment-related AE leading to discontinuation	35 (8)	16 (4)	189 (42)	136 (30)

- There were no treatment-related deaths in the NIVO group
- There were 2 (0.4%) treatment-related deaths in the IPI group (marrow aplasia and colitis), both >100 days after the last dose

Acceptable toxicity profile

Safety Summary

n (%)	NIVO (n = 452)		IPI (n = 453)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any AE	438 (97)	115 (25)	446 (98)	250 (55)
Treatment-related AE	385 (85)	65 (14)	434 (96)	208 (46)
Any AE leading to discontinuation	44 (10)	21 (5)	193 (43)	140 (31)
Treatment-related AE leading to discontinuation	35 (8)	16 (4)	189 (42)	136 (30)

- There were no treatment-related deaths in the NIVO group
- There were 2 (0.4%) treatment-related deaths in the IPI group (marrow aplasia and colitis), both >100 days after the last dose

KEYNOTE-54 (EORTC 1325) Study Schema

Randomized, phase 3 study of adjuvant PEMBRO after complete resection of high-risk stage III melanoma

- ≥ 18 year old with melanoma
- Complete surgical resection of stage III disease
- No ocular/mucosal melanoma
- No prior medical therapy for melanoma treatment
- No previous CTLA4 treatment

N = 1019

RANDOMIZED

1:1

Part 1: Post-surgical

PEMBRO 200 mg IV Q3 weeks: *up to 1 year*

PLACEBO IV Q3 weeks: *up to 1 year*

RECURRENCE

Part 2: Post-recurrence

Optional retreatment: PEMBRO 200 mg IV Q3 weeks: *up to 2 years*

Trial dates: 7/2015 – 7/2023 *(estimated)*

- **Primary endpoint:** RFS (6 months), RFS percentage with PD-L1 positive tumor expression.
- **Secondary endpoints:** DMFS and OS (overall vs PD-L1 tumor expression), AE

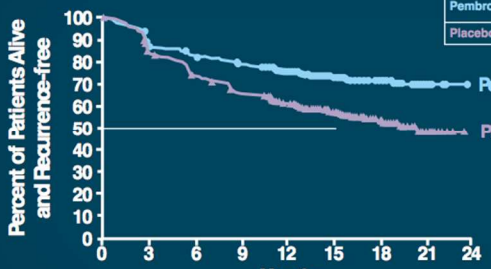
NCT02362594. Eggermont AMM, et al. *N Eng J Med.* 2018;378:1789-1801.

KEYNOTE-54 (EORTC 1325): RFS
ITT Population

Overall Intention-to-Treat Population

	Total No.	No. with Event	Hazard Ratio (98.4% CI)
Pembro	514	135	0.57 (0.43-0.74)
Placebo	505	216	1.00

P<0.001 by stratified log-rank test



No. at Risk									
Pembrolizumab	514	438	413	392	313	182	73	15	0
Placebo	505	415	363	323	264	157	60	15	0

RFS rates were longer for PEMBRO (71.4%) vs. PBO (53.2%) at 18 months, with distant metastasis incidence of 16.7% vs 29.7% respectively.

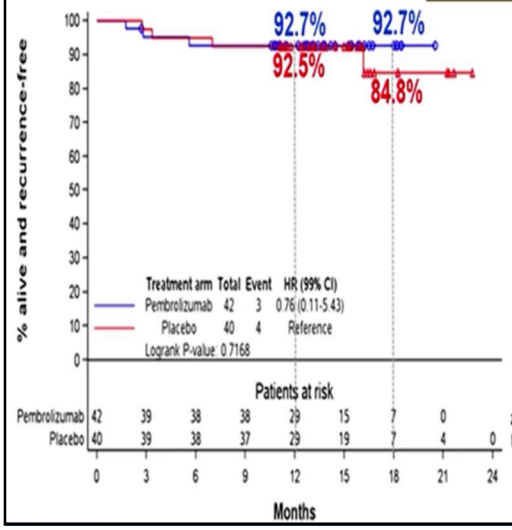
Eggermont AMM, et al. *N Eng J Med.* 2018;378:1789-1801.

Eggermont KN054 SMR 2018

Recurrence-Free Survival: subgroup analysis by AJCC-8

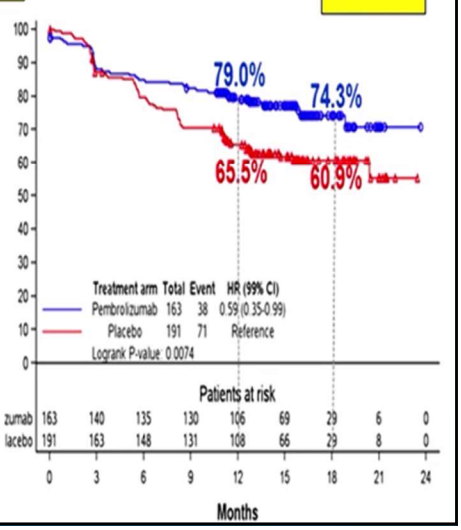
AJCC-8 Stage IIIA

HR 0.76



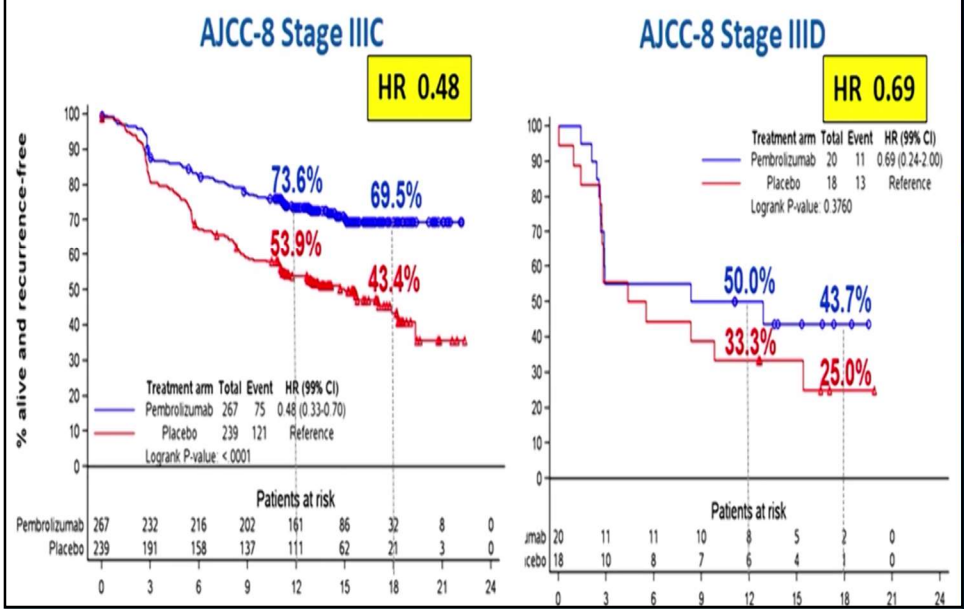
AJCC-8 Stage IIIB

HR 0.59



Eggermont KN054 SMR 2018

Recurrence-Free Survival: subgroup analysis by AJCC-8 (cont)



L. Eggermont AACR 2018

Patient Disposition and Treatment

	Pembrolizumab (N=514)	Placebo (N=505)
Started allocated treatment	N=509	N=502
Reasons for discontinuation, %	96.3%	98.8%
Normal completion	55.4	58.6
Disease recurrence	21.4	35.7
Adverse event	13.8	2.2
Patient/investigator decision	3.5	1.2
Other malignancy	0.8	1.0
Non-compliance/Other reason	1.3	0.2
Still on treatment, %	3.7	1.2
Median (IQR) doses received per patient	18 (9-18)	18 (8-18)

Event	Pembrolizumab (N = 509)		Placebo (N = 502)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any adverse event	475 (93.3)	161 (31.6)	453 (90.2)	93 (18.5)
Treatment-related adverse events†				
Any	396 (77.8)	75 (14.7)	332 (66.1)	17 (3.4)
Fatigue or asthenia	189 (37.1)	4 (0.8)	167 (33.3)	2 (0.4)
Skin reactions	144 (28.3)	1 (0.2)	92 (18.3)	0
Rash	82 (16.1)	1 (0.2)	54 (10.8)	0
Pruritus	90 (17.7)	0	51 (10.2)	0
Diarrhea	97 (19.1)	4 (0.8)	84 (16.7)	3 (0.6)
Arthralgia	61 (12.0)	3 (0.6)	55 (11.0)	0
Nausea	58 (11.4)	0	43 (8.6)	0
Dyspnea	30 (5.9)	1 (0.2)	15 (3.0)	0

Event	Pembrolizumab (N = 509)		Placebo (N = 502)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Immune-related adverse events, regardless of investigator attribution				
Any	190 (37.3)	36 (7.1)	45 (9.0)	3 (0.6)
Endocrine disorders	119 (23.4)	9 (1.8)	25 (5.0)	0
Hypothyroidism	73 (14.3)	0	14 (2.8)	0
Hyperthyroidism	52 (10.2)	1 (0.2)	6 (1.2)	0
Thyroiditis	16 (3.1)	0	1 (0.2)	0
Hypophysitis, including hypopituitarism	11 (2.2)	3 (0.6)	1 (0.2)	0
Type 1 diabetes mellitus	5 (1.0)	5 (1.0)	0	0
Adrenal insufficiency	5 (1.0)	1 (0.2)	4 (0.8)	0
Respiratory, thoracic and mediastinal disorders	24 (4.7)	4 (0.8)	3 (0.6)	0
Pneumonitis or interstitial lung disease	17 (3.3)	4 (0.8)	3 (0.6)	0
Sarcoidosis	7 (1.4)	0	0	0
Vitiligo or severe skin reactions	27 (5.3)	3 (0.6)	8 (1.6)	0
Vitiligo	24 (4.7)	0	8 (1.6)	0
Severe skin reactions	3 (0.6)	3 (0.6)	0	0
Gastrointestinal conditions	20 (3.9)	10 (2.0)	4 (0.8)	2 (0.4)
Colitis	19 (3.7)	10 (2.0)	3 (0.6)	1 (0.2)
Pancreatitis	2 (0.4)	1 (0.2)	1 (0.2)	1 (0.2)
Hepatobiliary disorders	9 (1.8)	7 (1.4)	1 (0.2)	1 (0.2)
Hepatitis	9 (1.8)	7 (1.4)	1 (0.2)	1 (0.2)
Other immune-related adverse events	15 (2.9)	5 (1.0)	5 (1.0)	0
Nephritis	2 (0.4)	2 (0.4)	1 (0.2)	0
Uveitis	2 (0.4)	0	0	0
Myositis	1 (0.2)	1 (0.2)	1 (0.2)	0
Myocarditis	1 (0.2)	1 (0.2)	0	0

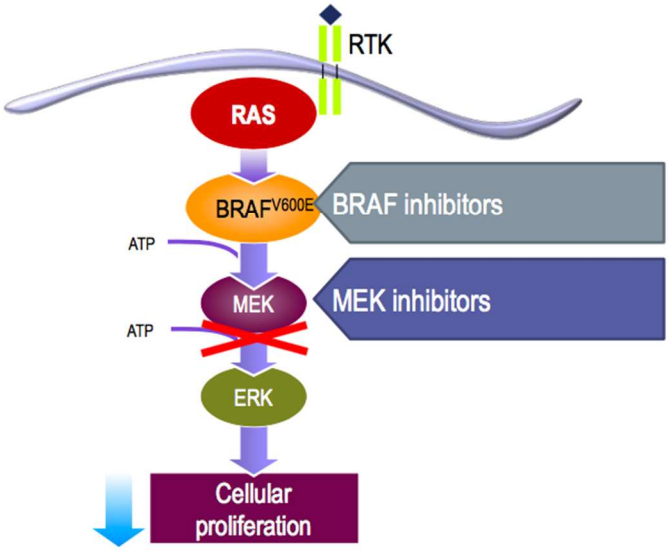
Adjuvant Nivolumab and Pembrolizumab

Effective in both BRAF mutated and wild-type melanoma pts in stage III/(IV)!

Well-tolerated in general (10-14% treatment discontinuations), but some rare, irreversible AEs

BRAF AND MEK INHIBITORS

Mechanism of action of BRAF and MEK inhibitors



BRAF MONOTHERAPY IN THE ADJUVANT SETTING

MADRID 2017 ESMO congress

BRIM8: a randomized, double-blind, placebo-controlled study of adjuvant vemurafenib in patients with completely resected *BRAF*$^{V600+}$ melanoma at high risk for recurrence

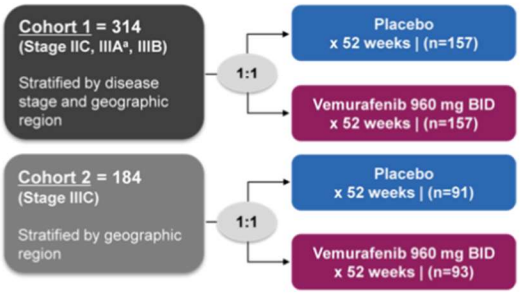
Karl Lewis,[1] Michele Maio,[2] Lev Demidov,[3] Mario Mandalà,[4] Paolo A. Ascierto,[5] Christopher Herbert,[6] Andrzej Mackiewicz,[7] Piotr Rutkowski,[8] Alexander Guminski,[9] Grant Goodman,[10] Brian Simmons,[10] Chenglin Ye,[10] Yibing Yan,[10] Dirk Schadendorf[11]

[1]University of Colorado Comprehensive Cancer Center, Aurora, CO, USA;[2]Division of Medical Oncology and Immunotherapy, Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy; [3]N N Blokhin Russian Cancer Research Center, Ministry of Health, Moscow, Russia; [4]Department of Oncology and Haematology, Papa Giovanni XXIII Cancer Center Hospital, Bergamo, Italy; [5]Melanoma Unit, Cancer Immunotherapy and Innovative Therapies, Istituto Nazionale Tumori Fondazione Pascale, Naples, Italy; [6]Bristol Haematology and Oncology Centre, Bristol, UK; [7]Department of Cancer Immunology, Poznan University for Medical Sciences, Med-POLONIA, Poznan, Poland; [8]Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie Institute – Oncology Center, Warsaw, Poland; [9]Melanoma Translational Research Group, Melanoma Institute Australia, Wollstonecraft, NSW, Australia; [10]Genentech, Inc., South San Francisco, CA, USA; [11]Department of Dermatology, University Hospital Essen, Essen, Germany; German Cancer Consortium, Heidelberg, Germany

BRAF MONOTHERAPY IN THE ADJUVANT SETTING

BRIM8 study design

Phase III, International, multicentre, double-blind, randomised, placebo-controlled study

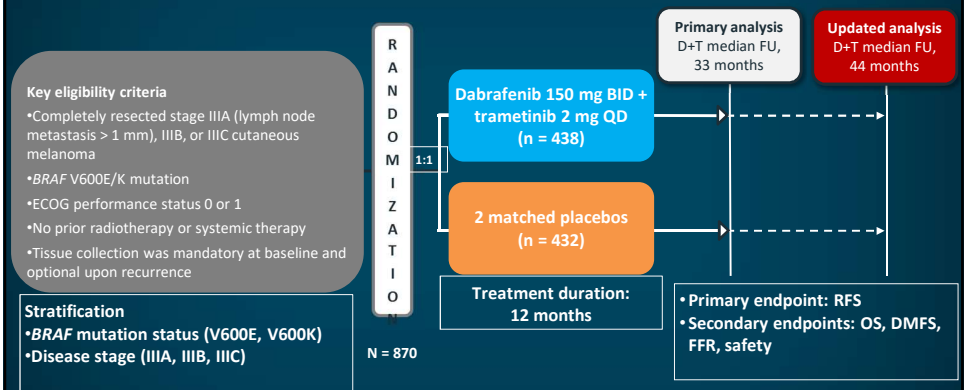


- **Primary endpoint**
  - DFS
- **Secondary endpoints**
  - DMFS
  - OS
  - Safety
  - HRQoL

BID, twice daily; DFS, disease-free survival; DMFS, distant metastasis-free survival; HRQoL, Health-related quality of life; OS, overall survival.
[a]Patients with stage IIIA melanoma were eligible if they had one or more nodal metastasis >1mm in diameter.

Presented by Lewis K at ESMO 2017. Courtesy of Dr Lewis

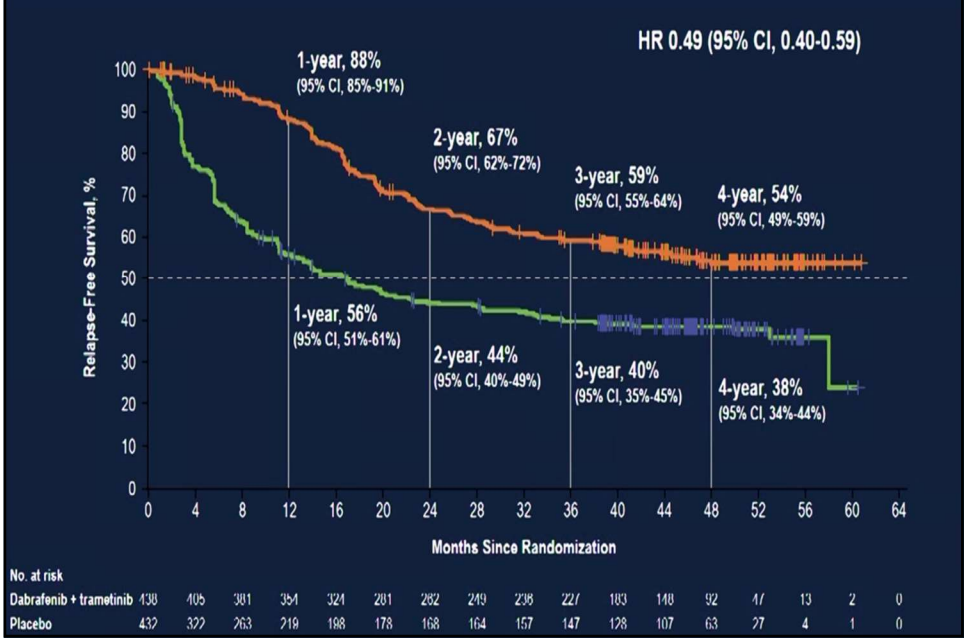
COMBI-AD: STUDY DESIGN—AND EXTENDED FOLLOW-UP ANALYSIS IN 2018



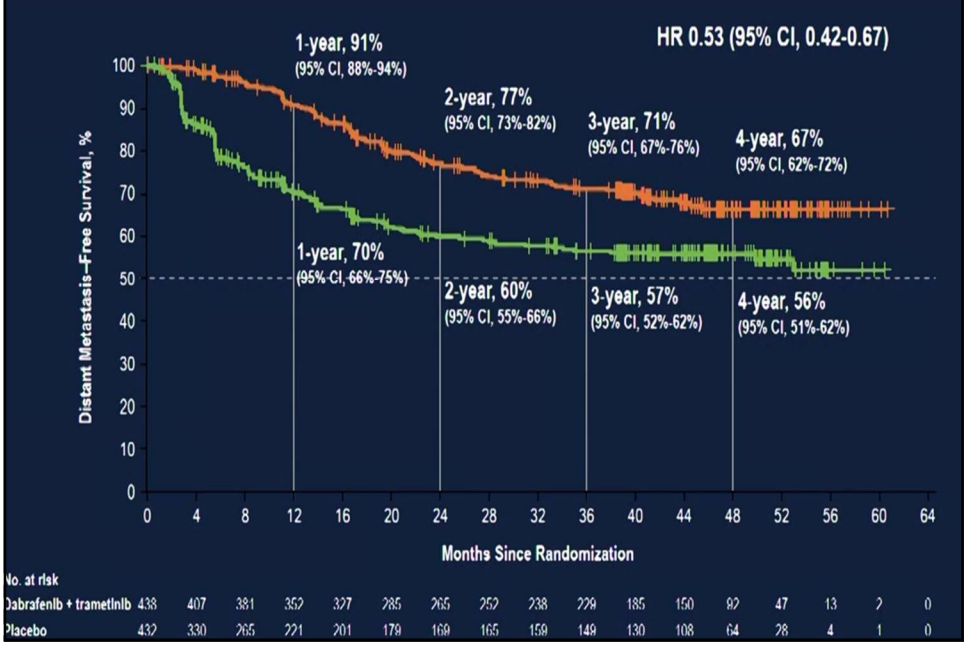
BID, twice daily; DMFS, distant metastasis–free survival; D+T, dabrafenib + trametinib; ECOG, Eastern Cooperative Oncology Group; FFR, freedom from relapse; FU, follow-up; QD, once daily.
Long GV, et al. *N Engl J Med*. 2017;377:1813-1823.

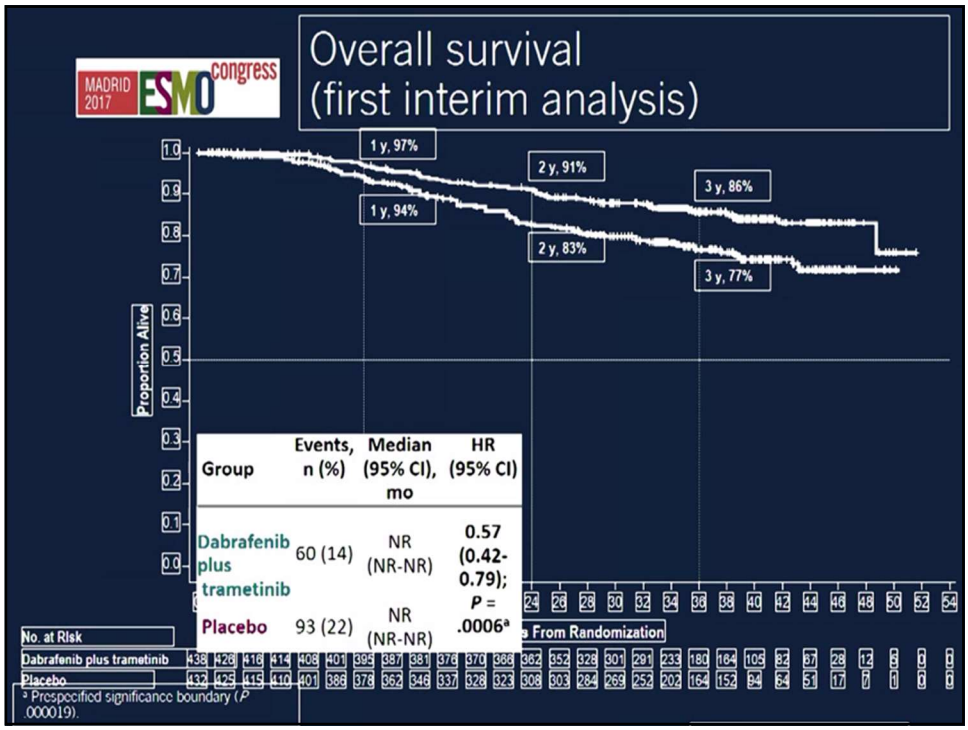
PRESENTED BY GV LONG AT ESMO 2018

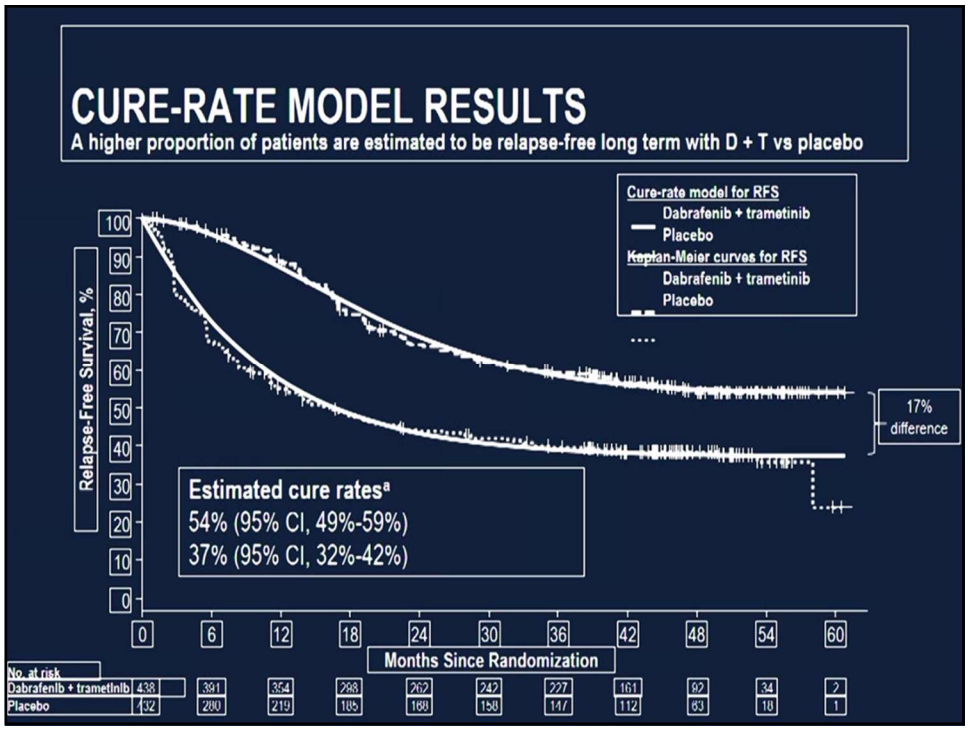
Relapse-Free survival

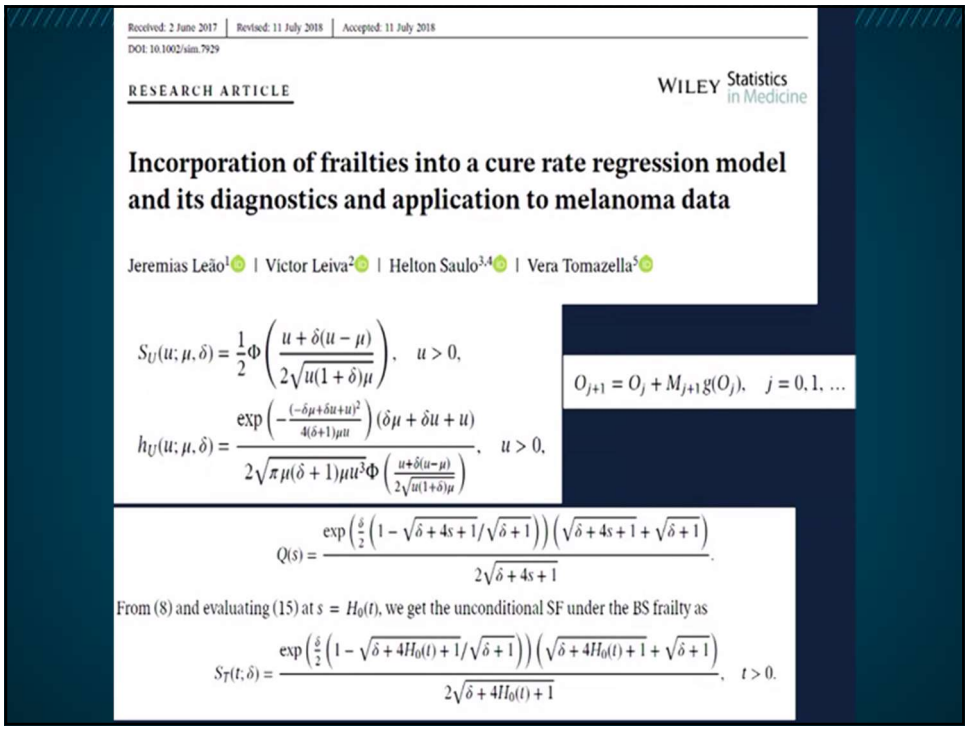


Distant metastasis–free survival




MADRID 2017
ESMO congress
Overall survival
(first interim analysis)
1 y, 97%
2 y, 91%
3 y, 86%
1 y, 94%
2 y, 83%
3 y, 77%
Proportion Alive
Group
Events, n (%)
Median (95% CI), mo
HR (95% CI)
Dabrafenib plus trametinib
60 (14)
NR (NR-NR)
0.57 (0.42-0.79); P = .0006[a]
Placebo
93 (22)
NR (NR-NR)
No. at Risk
Dabrafenib plus trametinib
Placebo
[a] Prespecified significance boundary (P .000019).


CURE-RATE MODEL RESULTS
A higher proportion of patients are estimated to be relapse-free long term with D + T vs placebo
Cure-rate model for RFS
Dabrafenib + trametinib
Placebo
Kaplan-Meier curves for RFS
Dabrafenib + trametinib
Placebo
Relapse-Free Survival, %
17% difference
Estimated cure rates[a]
54% (95% CI, 49%-59%)
37% (95% CI, 32%-42%)
Months Since Randomization
No. at risk
Dabrafenib + trametinib 438 391 354 288 262 242 227 161 92 34 2
Placebo 432 280 219 185 168 158 147 112 63 18 1



Received: 2 June 2017 | Revised: 11 July 2018 | Accepted: 11 July 2018
DOI: 10.1002/sim.7929

RESEARCH ARTICLE

WILEY Statistics in Medicine

Incorporation of frailties into a cure rate regression model and its diagnostics and application to melanoma data

Jeremias Leão[1] | Víctor Leiva[2] | Helton Saulo[3,4] | Vera Tomazella[5]

$$S_U(u;\mu,\delta) = \frac{1}{2}\Phi\left(\frac{u+\delta(u-\mu)}{2\sqrt{u(1+\delta)\mu}}\right), \quad u>0,$$

$$h_U(u;\mu,\delta) = \frac{\exp\left(-\frac{(-\delta\mu+\delta u+u)^2}{4(\delta+1)\mu u}\right)(\delta\mu+\delta u+u)}{2\sqrt{\pi\mu(\delta+1)\mu u^3}\Phi\left(\frac{u+\delta(u-\mu)}{2\sqrt{u(1+\delta)\mu}}\right)}, \quad u>0,$$

$$O_{j+1} = O_j + M_{j+1}g(O_j), \quad j = 0, 1, \ldots$$

$$Q(s) = \frac{\exp\left(\frac{\delta}{2}\left(1-\sqrt{\delta+4s+1}/\sqrt{\delta+1}\right)\right)\left(\sqrt{\delta+4s+1}+\sqrt{\delta+1}\right)}{2\sqrt{\delta+4s+1}}.$$

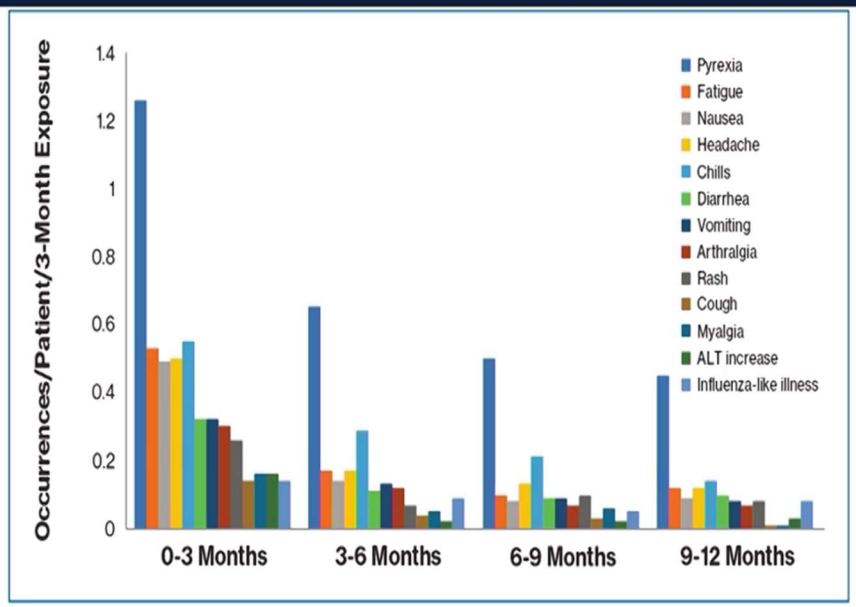
From (8) and evaluating (15) at $s = H_0(t)$, we get the unconditional SF under the BS frailty as

$$S_T(t;\delta) = \frac{\exp\left(\frac{\delta}{2}\left(1-\sqrt{\delta+4H_0(t)+1}/\sqrt{\delta+1}\right)\right)\left(\sqrt{\delta+4H_0(t)+1}+\sqrt{\delta+1}\right)}{2\sqrt{\delta+4H_0(t)+1}}, \quad t>0.$$

Safety summary

AE Category, n (%)	Dabrafenib Plus Trametinib (n = 435)	Placebo (n = 432)
Any AE	422 (97)	380 (88)
AEs related to study treatment	398 (91)	272 (63)
Any grade 3/4 AE	180 (41)	61 (14)
Any SAE	155 (36)	44 (10)
SAEs related to study treatment	117 (27)	17 (4)
Fatal AEs related to study drug	0	0
AEs leading to dose interruption	289 (66)	65 (15)
AEs leading to dose reduction	167 (38)	11 (3)
AEs leading to treatment discontinuation[a]	114 (26)	12 (3)

Any Occurence (exposure-adjusted) of AEs (≥15% of patients) Over Time in Patients Who Received Dabrafenib Plus Trametinib

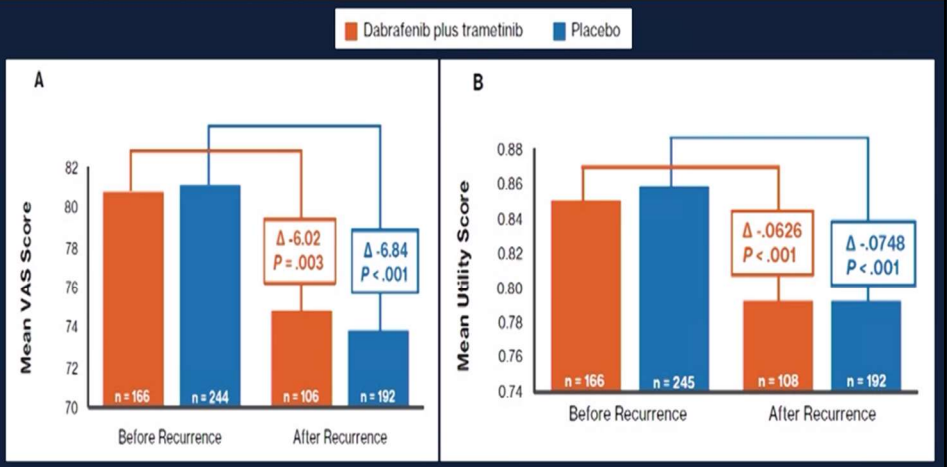


AE, adverse event.

Table 2. AEs Leading to Discontinuation (≥ 1% of patients)

	Dabrafenib + Trametinib N = 435	Placebo N = 432
Patients with any AE leading to discontinuation[a]	**114 (26)**	**12 (3)**
Pyrexia	**38 (9)**	**0**
Chills	**16 (4)**	**0**
Fatigue	8 (2)	0
ALT increase	7 (2)	0
Headache	6 (1)	0
Arthralgia	5 (1)	0
AST increase	5 (1)	0
Nausea	5 (1)	1 (< 1)
Neutropenia	5 (1)	0

Mean EQ-5D VAS (A) and Utility (B) Scores at Assessments Before and After Recurrencea



P value was calculated using a paired *t* test.
[a] Regardless of whether recurrence occurred during or after the end of treatment.

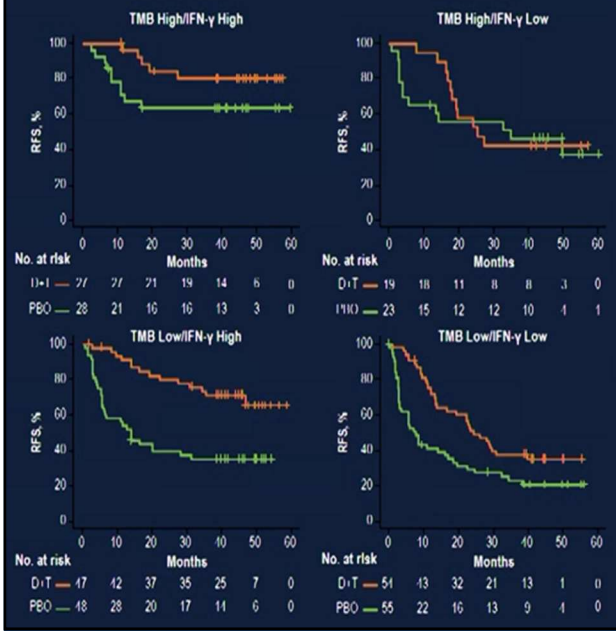
Schadendorf et al. Effect on Health-Related Quality of Life of Adjuvant Treatment With Dabrafenib Plus Trametinib in Patients With Resected Stage III BRAF-Mutant Melanoma. Presented at ASCO 2018. Abstract 9591.

Adjuvant Dabrafenib and Trametinib: highly effective and relatively well tolerated (good QoL despite 26% treatment discontinuations)!

Adjuvant Melanoma Therapy:new jobs to do!

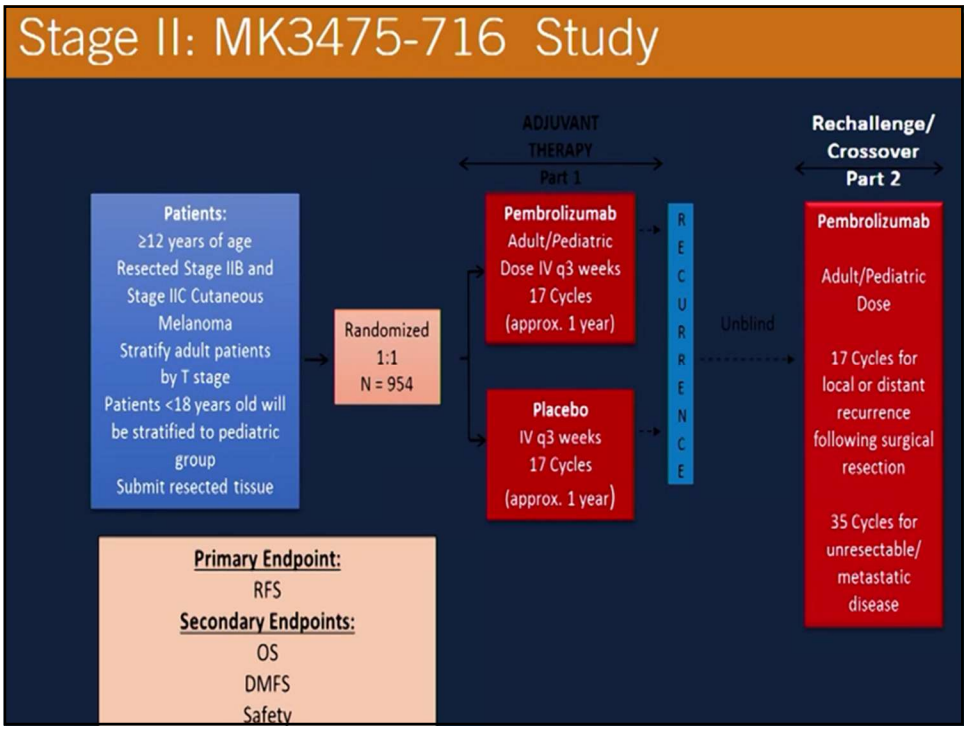
- Testing the new drugs for AJCC stage 2 melanomas („how much recurrence risk justifies how much risk for toxicities?“)
- Biomarker development for the selection of the best patients (and prediction of certain toxicities)
- Addressing the issue of induction for resistance for potential stage IV setting
- Neoadjuvant trials are mandatory!

EXPLORATORY ANALYSIS OF THE PREDICTIVE VALUE OF TMB/Ifn-γ

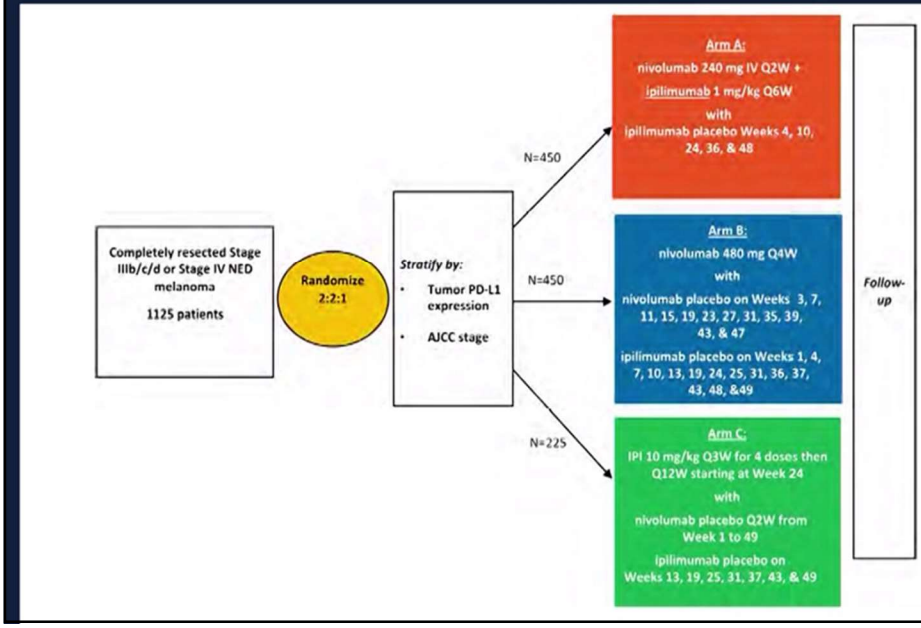


The analysis was not powered to assess treatment interactions, but results suggest that low TMB or high TMB/high IFN-γ may be associated with greater RFS benefit than high TMB/low IFN-γ

Stage II: MK3475-716 Study



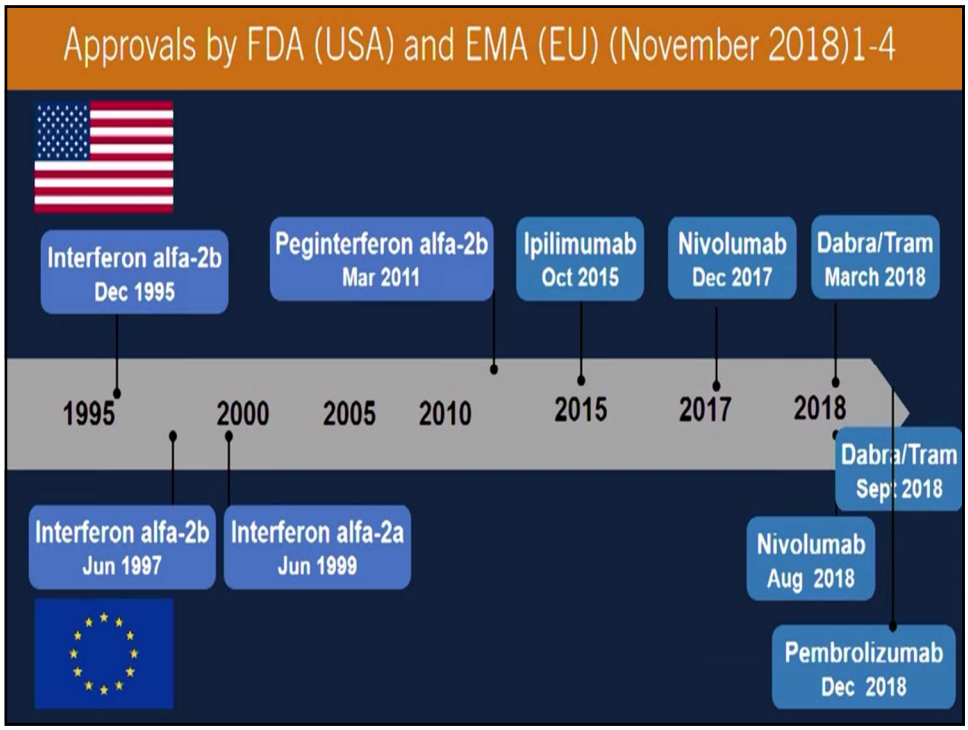
Ipi/Nivo combo: CA209-915 trial



	BRIM-8	Checkmate-238	Nivo+Ipi	Combi-AD	Keynote-054	EORTC 18071 - Ipi
Patients	IIc – IIIc (SN >1mm)	IIIB, IIIc or IV (no brain mets)	IIIc or IV (No Brain mets)	IIIA (>1mm), IIIB, IIIC	IIIA (>1mm), IIIB, IIIc (no Intransits)	IIIA (>1mm), IIIB, IIIC (no intransits)
Mucosal melanoma	excluded	3%	excluded	excluded	excluded	excluded
Duration of therapy	1 yr	1 yr	1 yr	1 yr	1 yr	1 yr
RFS	2yr DFS: 46.3% Vs 47.5% (IIIc)	1 yr 70% vs 60% HR 0.65	75 -80% at 2 yrs	3 yr 58% vs 39% HR 0.57	1 yr 75% vs 61% HR 0.57	5 yr 40% vs 30% HR 0.75
DMFS	NA	HR 0.73	NA	HR 0.51	NA	5yr 48% vs 38%
OS	NA	NA	NA	3 yr 86% vs 77% HR 0.57	NA	5yr 65% vs 54%

Patient selection for adjuvant treatment: potential criteria apart from efficacy

- **Patient characteristics**: age/gender
- Performance status
- Comorbidities
- **Tumor characteristics**: stage of metastasis (AJCC)
- Micro- versus macrometastases
- Mutational status
- Biomarkers (PD-L1 status)
- **Treatment factors**: oral vs. IV (intervals?)
- Potential toxicities (reversible vs irreversible)


Approvals by FDA (USA) and EMA (EU) (November 2018)1-4
Interferon alfa-2b
Dec 1995
Peginterferon alfa-2b
Mar 2011
Ipilimumab
Oct 2015
Nivolumab
Dec 2017
Dabra/Tram
March 2018
1995
2000
2005
2010
2015
2017
2018
Dabra/Tram
Sep: 2018
Interferon alfa-2b
Jun 1997
Interferon alfa-2a
Jun 1999
Nivolumab
Aug 2018
Pembrolizumab
Dec 2018


For more information visit conference web site:
www.seic2019.com
1st
SOUTHEASTERN EUROPE IMMUNOTHERAPY CONFERENCE
Zagreb, 11-12 October 2019
Hotel Dubrovnik
Dear friends
On behalf of the 1st Southeastern European Immunotherapy Conference Organizing Committee, it is my great pleasure to invite you to the conference to be held on 11-12 October 2019 in Zagreb, Croatia.
We hope that you will enjoy the conference and that your interaction with your colleagues from many different countries will stimulate a creative exchange of ideas and will be personally rewarding.
We thank you in advance for being part of this conference and hope to make the 1st Southeastern European Immunotherapy Conference in Zagreb a memorable experience for you.
Davorin Herceg, MD, PhD

Melanoma 2020: standards of care and unmet needs

Prof dr Lidija Kandolf Sekulović
Medical Faculty, Medical Military Academy
Belgrade, Serbia

Metastatic melanoma: standards of care

SURGERY:
For solitary metastases: PET-CT and brain MRI necessary before decision for surgery (+adjuvant therapy with anti-PD1)

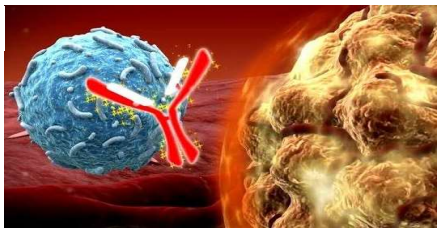
SYSTEMIC THERAPY:
- Checkpoint inhibitor immunotherapy: anti-PD1 antibodies, anti-CTLA4 antibody
- Targeted therapy: BRAF and MEK inhibitors

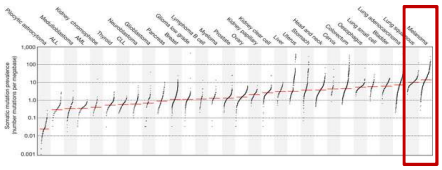
RADIOTHERAPY :
STEREOTACTIC RADIOTHERAPY AND GAMMA KNIFE SURGERY for CNS and other distant sites
Palliative for bone metastases, lymph nodes and soft tissues, CNS metastases

SUPPORTIVE CARE

Systemic treatment of metastatic melanoma 2019

BRAF gene mutation
early event in oncogenesis





High mutational load =
Immunotherapy effective

Targeted therapy

Vemurafenib
Cobimetinib
Dabrafenib
Trametinib
Encorafenib
Binimetinib

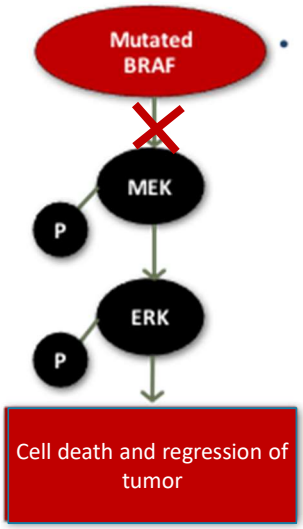
Checkpoint inhibitors

Ipilimumab
Nivolumab
Pembrolizumab
Atezolizumab
Avelumab
Durvalumab

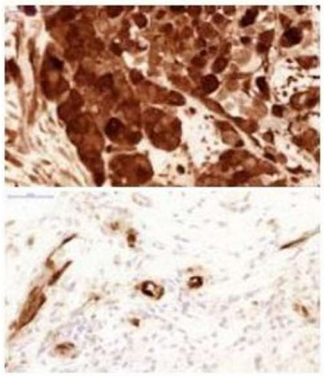
FDA APPROVED

EMA APPROVED

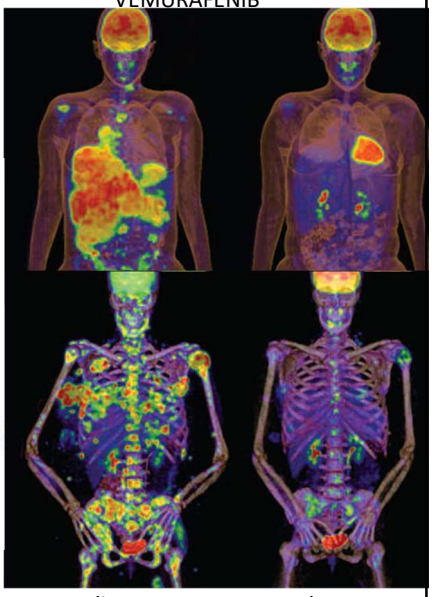
BRAF INHIBITOR



- Constant activation without control



VEMURAFENIB



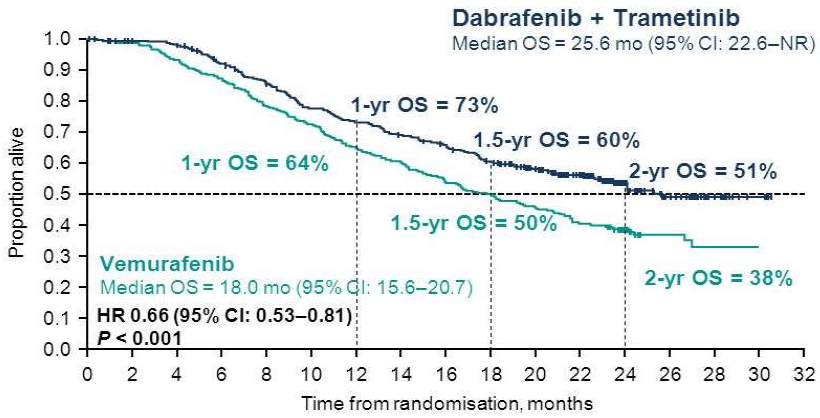
Baseline 15 days

BRAF inhibitor: treatment resistance

(Wagle et al, 2011, J Clin Oncol 29:3085)

- Strong initial effects vemurafenib
- Emerging drug resistancy
- Reccurence of aggressive tumors

Dabrafenib trametinib versus vemurafenib



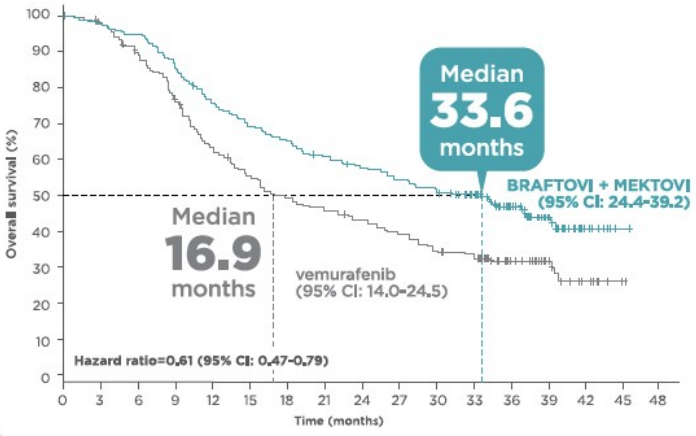
Patients at risk[a]

enib + Trametinib	352	342	336	311	286	260	245	230	217	198	173	128	68	38	16	5	0
Vemurafenib	352	341	315	286	252	231	201	187	166	152	129	88	46	28	7	0	0

off: March 2015.

5

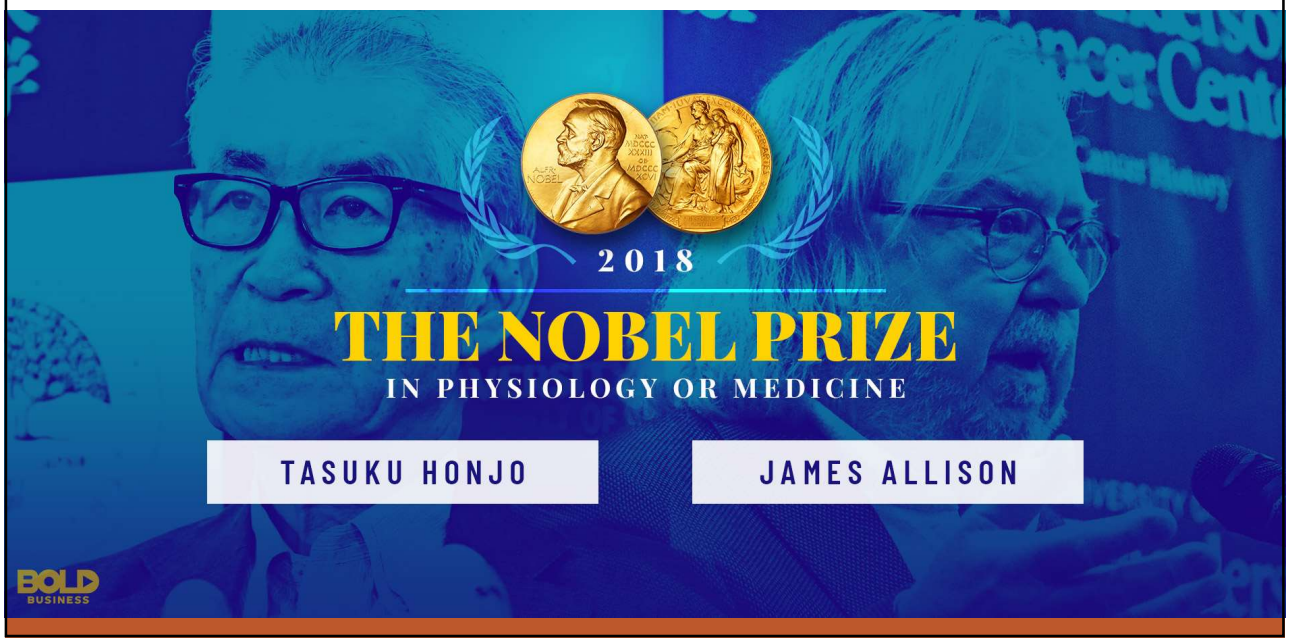
Encorafenib binimetinib versus vemurafenib

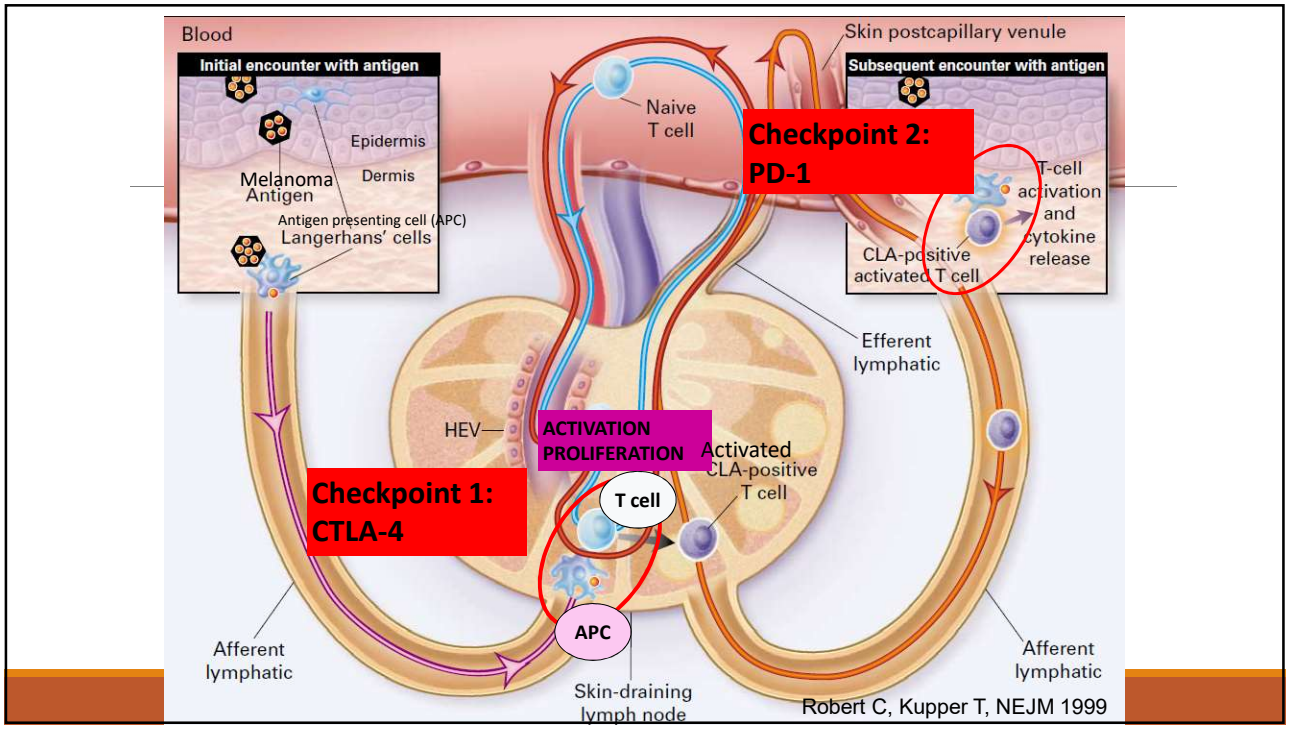


Number at risk

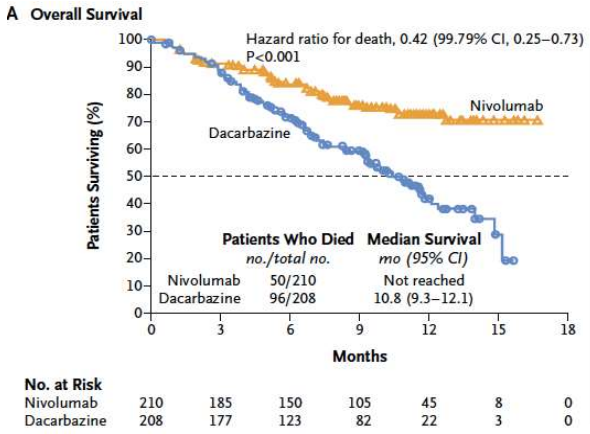
BRAFTOVI + MEKTOVI	192	188	182	166	144	132	124	115	108	102	95	82	57	30	9	1	0
vemurafenib	191	184	166	140	115	100	89	83	77	71	62	56	30	19	8	1	0

Checkpoint inhibitor immunotherapy: anti-PD1 and anti-CTLA4

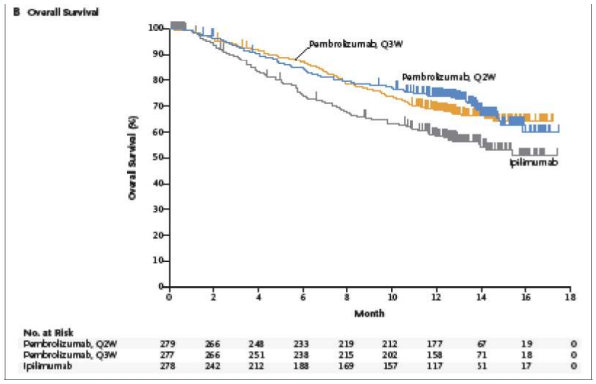




Anti PD1: efficacy

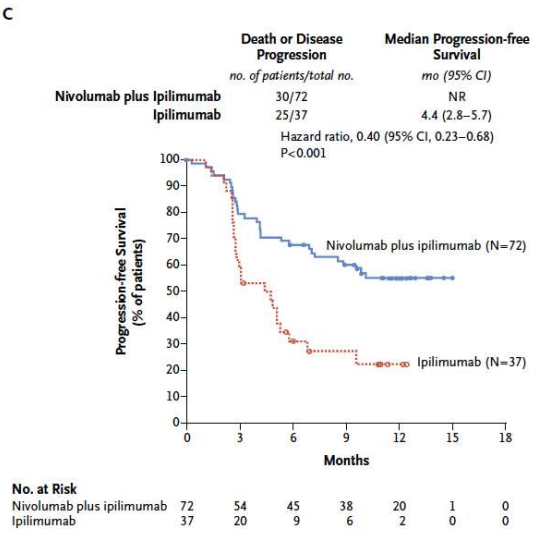


Robert C et al. N Engl J Med 2015;372:320-30.



Robert C et al. N Engl J Med 2015;372:2521-32.

Combination immunotherapy: anti-PD1 plus anti CTLA4



EMA, April 2016

anti-PD1+anti-CTLA4:

- Higher response rates
- Faster response
- Long-term responses
- More frequent and more severe side effects

Postow M et al. N Engl J Med 2015;372:2006-17.

Brain metastases

STAGE III: **10-13%** of patients already have CNS mets (CT/MRI necessary in follow-up!)

STAGE IV: **18-46%**

ON AUTOPSY **55-75%**

Frequent relapses in patients with regression of internal organ metastases

Overall survival: 4 months after diagnosis *(Fife et al, J Clin Oncol 2004)*

Fife KM. J Clin Oncol 2004; Sawaya RE, Brain Tumors. Philadelphia; 2001. Barnholtz-Sloan JS, 2004; Harrison BE, Am J Clin Oncol 2003;

The majority of patients with metastatic melanoma are not represented in pivotal phase III immunotherapy trials

Marco Donia [a,b,*], Marie Louise Kimper-Karl [c], Katrine Lundby Høyer [d], Lars Bastholt [c], Henrik Schmidt [d], Inge Marie Svane [a,b]

Table 2
Eligibility criteria in patients with MM (n = 276).

Performance status	PS ≥ 2 81 (29.3%)
Brain metastases	Yes, active 62 (22.5%)
Comorbidities	Yes 58 (21.0%)
Other malignancies	Yes 24 (8.7%)
Autoimmunity	Yes 12 (4.3%)
Immunosuppression	Yes 46 (16.7%)

MM, metastatic melanoma.

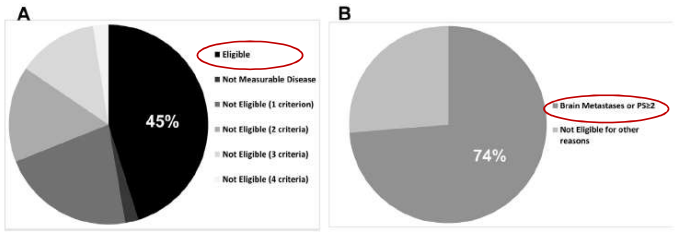


Fig. 1. Common eligibility criteria for immunotherapy trials may exclude over half of the patients diagnosed with metastatic m
(A) The proportion of 'eligible' patients as well as 'not eligible' patients, because they do not meet one, two or more pre-defined
criteria is shown. (B) About three quarters of patients 'not eligible' have PS ≥ 2 or active/untreated brain metastases.

Brain metastases

HIRURGIJA	**8.7 meseci**
Hirurgija + radioterapija celog mozga (WBRT)	**8.9 meseci**
Samo radioterapija celog mozga (WBRT)	**3.4 meseci**
Suportivna terapija	**2.1 meseci**

STEREOTAKSNA RADIOHIRURGIJA:
Lokalna kontrola bolesti 90% slučajeva
Efikasnost slična hirurgiji
Ukupno preživljavanje 5-11 meseci

Clinical outcomes of melanoma brain metastases treated with stereotactic radiation and anti-PD-1 therapy

K. A. Ahmed[1], D. G. Stallworth[2], Y. Kim[3], P. A. S. Johnstone[1], L. B. Harrison[1], J. J. Caudell[1], H. H. M. Yu[1], A. B. Etame[4], J. S. Weber[5] & G. T. Gibney[6,7*]

Annals of Oncology 27: 434–441, 2016

Timing of SRS		
During anti-PD-1	5	7
Before anti-PD-1	33	45
After anti-PD-1	35	48
No. of patients		26

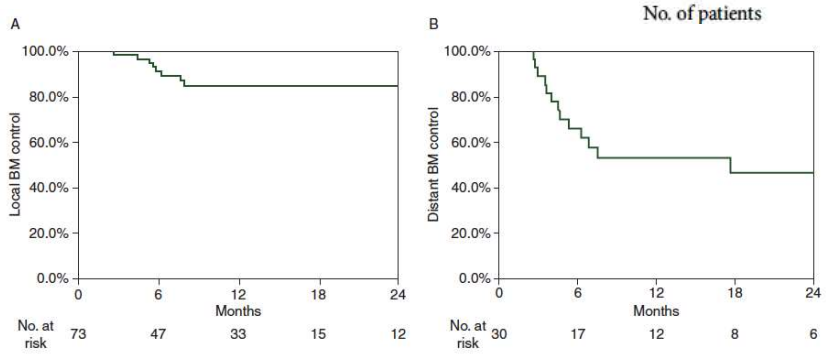


Figure 1. A) Kaplan–Meier curve for local BM control of 73 treated lesions and B) distant BM control following 30 treatment sessions.

Survival of patients with melanoma brain metastasis treated with stereotactic radiosurgery and active systemic drug therapies

European Journal of Cancer 75 (2017) 169–178

Ee Siang Choong [a], Serigne Lo [b], Martin Drummond [b], Gerald B. Fogarty [b,d,e], Alexander M. Menzies [b,e,f], Alexander Guminski [b,e,f], Brindha Shivalingam [b,e,e], Kathryn Clarke [d], Georgina V. Long [b,e,f], Angela M. Hong [b,d,e,e]

Method: A total of 108 patients treated with SRS from 2010 to 2015 were included. Systemic treatment use within 6 weeks of SRS was noted. OS was defined as time from SRS to death or last follow-up, and BC was defined as absence of any active intracranial disease during follow-up. Univariate and multivariate Cox proportional hazard analyses were performed on clinico-pathological prognostic features associated with OS and BC.

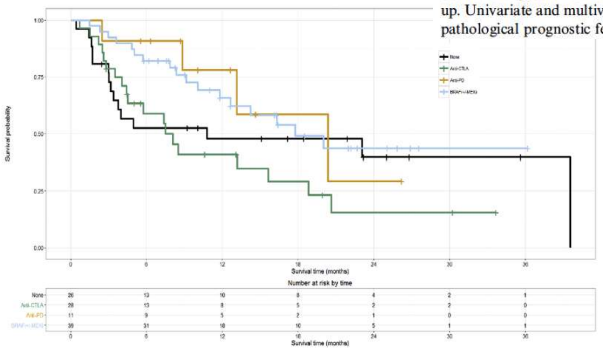


Fig. 1. Kaplan Meier plot for OS according to types of systemic treatment received – anti-CTLA4, anti-PD1 and BRAFi ± MEKi (n = 104). •The one patient who had MEKi alone was excluded in the survival analysis.

Table 5
Trials and retrospective series of systemic drug therapies in patients with active brain metastases.

Systemic therapy	Study	Year	No. of patients	Patients received SRS	Systemic therapy	Median OS	OS at 6 months	OS at 1 year	OS at 2 years
Anti-CTLA4	Choong *et al.*		28	Y	Ipilimumab	7.5	59%	41%	16%
	Kiess [26]	2014	46	Y	Ipilimumab	12.4	N/A	40–65%	N/A
	Knisely [14]	2012	27	Y	Ipilimumab	21.3	N/A	N/A	47.2%
	Mathew [34]	2013	25	Y	Ipilimumab	5.9	56%	N/A	N/A
	Margolin [15]	2012	72	N	Ipilimumab				
			51	Asymptomatic (cohort A)		7.0	55%	31%	26%
			21	Symptomatic (cohort B)		3.7	38%	19%	10%
Anti-PD1	Choong *et al.*		11	Y	Anti-PD1	20.4	91%	78%	29%
	Ahmed [27]	2016	19	Y	Nivolumab	11.8	78%	55%	N/A
BRAFi ± MEKi	Choong *et al.*		39	Y	BRAFi ± MEKi	15.6	82%	66%	44%
	Ly D [30]	2015	52	Y	BRAFi	11.2	N/A	N/A	N/A
	Wolf [31]	2015	31	Y	BRAFi – (23% MEKi)	11.2	54%	41%	N/A
	Ahmed [29]	2015	24	Y	BRAFi	7.2	N/A	N/A	N/A
	Patel [36]	2016	6	Y	BRAFi + MEKi	20.0	N/A	100%	N/A
	Long [21]	2012	172	N	BRAFi				
			89	No prior local therapy (cohort A)		8.3	61%	N/A	N/A
			83	Progressed after local therapy (cohort B)		7.9	61%	N/A	N/A

OS, overall survival; N/A, not reported.
Only trials or series with reported relevant endpoints included.

Anti CTLA4 i anti PD1 u metastazama mozga (IVD)

	Cohort A		Cohort B		Cohort C (n=16)
	Drug* naive (n=27)	Overall (n=35)	Drug* naive (n=19)	Overall (n=25)	
Intracranial response					
Overall (%; 95% CI)	15 (56%; 35–75)	16 (46%; 29–63)	4 (21%; 6–46)	5 (20%; 7–41)	1 (6%; 0–30)
Complete response	5 (19%)	6 (17%)	2 (11%)	3 (12%)	0
Partial response	10 (37%)	10 (29%)	2 (11%)	2 (8%)	1 (6%)
Stable disease	3 (11%)	4 (11%)	0	0	2 (13%)
Progressive disease	8 (30%)	14 (40%)	14 (74%)	19 (76%)	13 (81%)
Non-evaluable	1 (4%)	1 (3%)	1 (5%)	1 (4%)	0

Side effects?

Class specific

- Targeted therapy: primary drug target/pathway in cancer cells/tissues also mediates physiologic functions in normal cells/tissues.
- Checkpoint inhibitors: immune-mediated adverse effects; monoclonal antibody administration related side efects

Drug specific

- Other mechanisms
  - Vemurafenib: photosensitivity
  - Dabrafenib: Hemolytic anemia in patients with G6PD deficiency (dabrafenib has sulfonamide moiety)

Tumor specific:

- different frequencies of side effects of the sam drug in different tumors

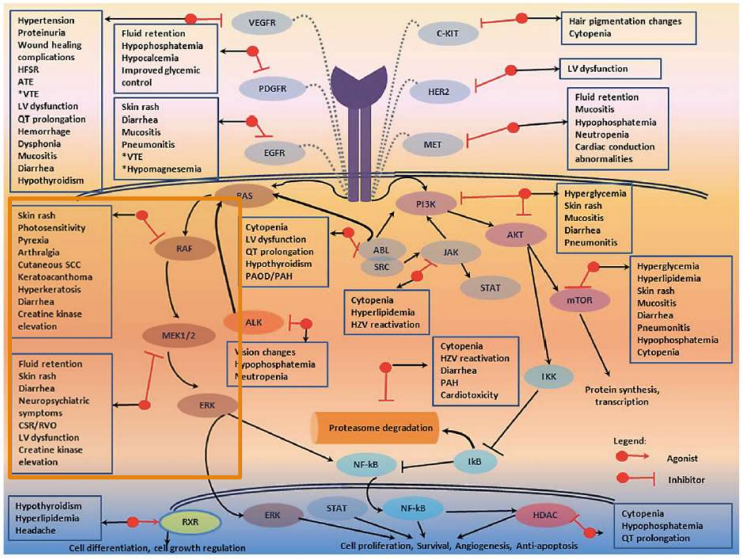


FIGURE 1. Toxicities Associated With Signal Transduction Inhibitors.*Associated predominantly with monoclonal antibodies. ATE indicates arterial thromboembolism; CSR, central serous retinopathy; HZV, herpes zoster virus; LV, left ventricular; PAH, pulmonary arterial hypertension; PAOD, progressive arterial occlusive disease; RVO, retinal vein occlusion; SCC, squamous cell cancer; VTE, venous thromboembolism.

CA CANCER J CLIN 2013;63:249–279

Targeted therapy toxicity

- Paradoxical activation of MAPK pathway in BRAFwt cells
- Additional oncogene mutations (Ras, p53, TGF-beta) or HPV cofactors
- Paradoxical cell proliferation
- Class effect

Targeted therapy: side-effects
all grades % (grade 3-4 %)

	Vemurafenib	Dabrafenib	Encorafenib	Trametinib	Vemurafenib Cobimetinib	Dabrafenib Trametinib	Encorafnib Binimetinib (450)
Rash	68 (16)	30 (0)	45 (5)	57 (8)	73 (17)	27 (0)	23 (1)
Cutaneous SCC	21 (21)	10 (4)	9 (1)	0	6 (5)	7 (5)	4 (0)
Diarrhoea	33 (1)	8 (0.4)	14 (2)	43 (0)	33.3 (7)	36 (2)	36 (3)
Arthralgia	56 (6)	19 (<1)	44 (9)	NR	38 (3)	24 (0)	26 (1)
Fatigue	33 (3)	18 (1)	25 (1)	26 (4)	37 (5)	53 (4)	29 (2)
Nausea	37.3 (1)	13 (0.4)	NR	18 (1)	41.3	36(0.4)	NR
Vomiting	14 (1)	7 (<1)	NR	13 (1)	24.3	30.3 (0.4)	NR
Cardiac	10 (2)	3 (2)	2 (1)	7 (1)	17 (3)	9 (0)	8 (2)
Ophtalmologic	9 (4)	2 (0)	1 (0)	9 (<1)	27 (3)	2 (2)	13 (2)
Liver laboratry abnormalities	36 (11)	26 (2)	7 (2)	24 (2)	26 (11)	27(2)	14 (6)
CPK increase	3 (<1)	NR	1 (0)	NR	35 (12)	2.9	23 (7)
Photosensitivity	41.4(4)	3 (0)	4 (0)	NR	28 (2)	4 (0)	5 (1)
Pyrexia	22.8 (<1)	32(4)	15 (1)	NR	26 (2)	52 (7)	18 (4)

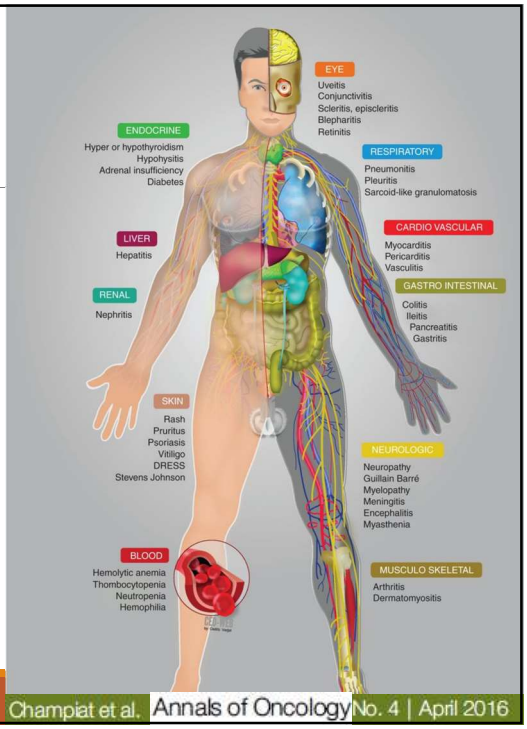
Checkpoint-inhibitors: immune-related adverse effects

Inhibitory immune-checkopoints are associated with tolerance mechanisms and prevention of autoimmunity

In the setting of CTLA-4 and anti-PD1-PDL-1 blockade immune related adverse events develop

Most frequent: skin ,GI, liver, endocrine

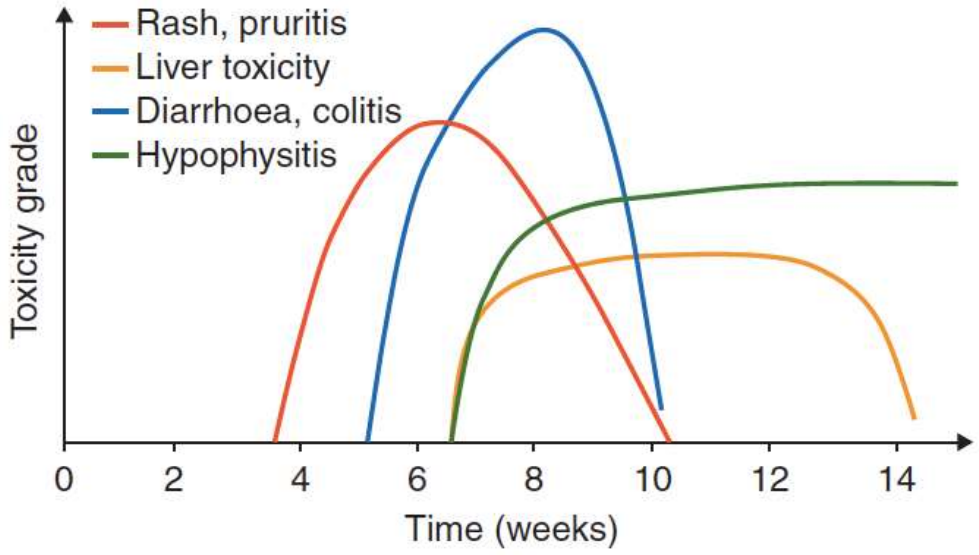
Less common: pneumonitis, neurotoxicity, ocular, etc.



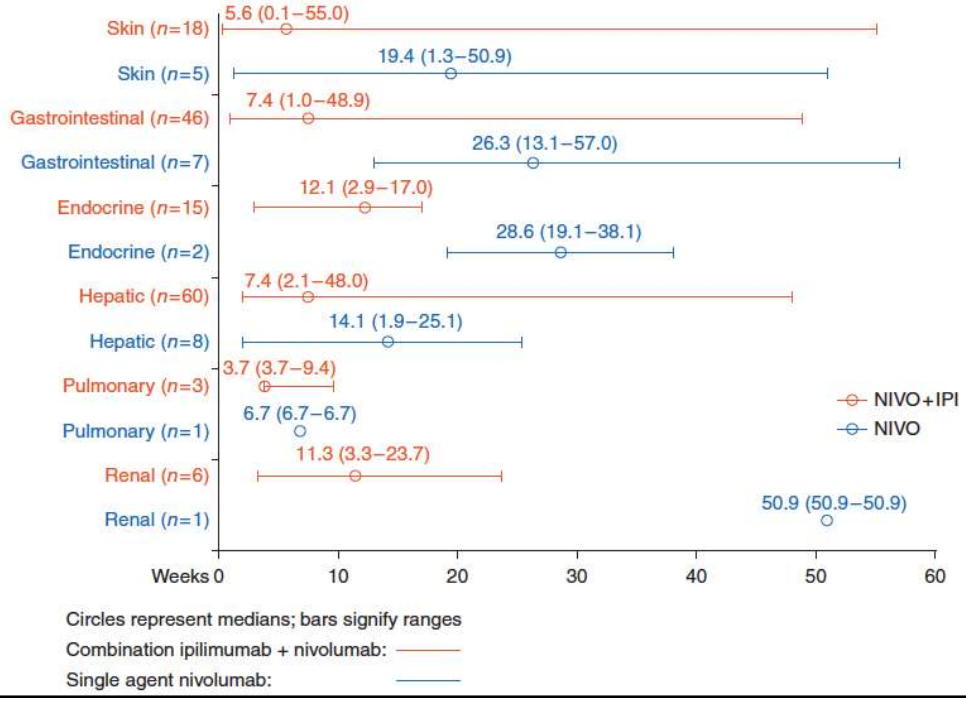
Champiat et al. Annals of Oncology No. 4 | April 2016

Immune related side effects: frequency

	Ipilimumab all % (gr 3-4%)	**Nivolumab** all, % (gr 3-4%)	**Pembroiizumab** all % (gr 3-4, %)	**Nivolumab Ipilimumab** all % (gr 3-4%)
Skin Rash Pruritus	54.6 (2.5) 21.6 (1.4) 34.4 (0.3)	38.4 (1.1) 16.9 (0.4) 18.4 (0.1)	 21 (1) 21 (1)	61.9 (6.4) 31.2 (3.2) 33.4 (1.7)
Gastrointestinal Diarrhea Colitis	42.3 (11.5) 43 (8.8) 14 (9.6)	17.7 (1.7) 17.2 (1.3) 1.1 (0.6)	 20 (1)	46.4 (15.7) 33.6 (6.2) 11.8 (8.4)
Pulmonary Pneumonitis	2.2 (0.6) 2 (0.6)	2 (0.1) 1.8 (0.1)	 4 (1)	7.6 (1.2) 6.9 (1.2)
Endocrine Thyroid Hypophisitis	11.8 (2.5) 6.4 (0) 4.2 (2.2)	10.8 (0.6) 10.1 (0.1) 0.4 (0.3)	 8 (1) NR	29.7 (4.9) 18.9 (0.9) 8.6 (1.7)
Renal	NR	1.5 (0.5)	2 (1)	4.7 (1.7)
Hepatic Lab abnormal.	0.7 (0.1) NR	6.9 (2.2) 0.4 (0.1)	 18(1)	29 (17.4) 18.2 (8.4)
Infusion reactions	NR	4.8 (0.3)	NR	2.5 (0)
irAE	**86.2 (27.7)**	**86.3 (20.8)**		**95.8 (58.5%)**
Treatment discontinuation	**16.1 (14.1)**	**11.5 (7.7)**		**39.6 (31)**



Puzanov *et al. Journal for ImmunoTherapy of Cancer* (2017) 5:95



Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: a systematic review

Annals of Oncology 28: 2377–2385, 2017

L. Khoja[1,2†], D. Day[3,4,5†], T. Wei-Wu Chen[6,7,8], L. L. Siu[3,4] & A. R. Hansen[3,4*]

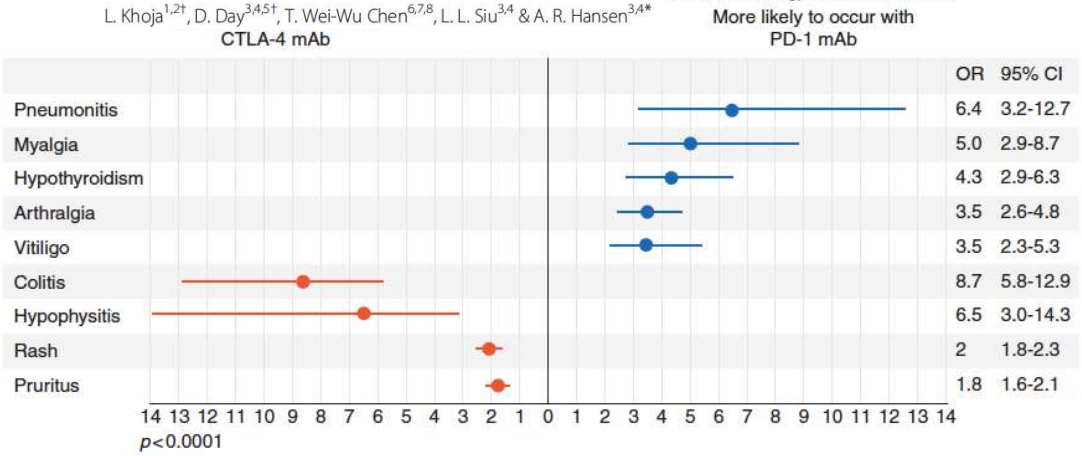


Figure 2. The odds ratio (OR) of different immune-related adverse events (all grades) comparing PD-1/PD-L1 versus CTLA-4 immune checkpoint inhibitors.

Annals of Oncology 28 (Supplement 4): iv119–iv142, 2017
doi:10.1093/annonc/mdx225

CLINICAL PRACTICE GUIDELINES

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

J. B. A. G. Haanen[1], F. Carbonnel[2], C. Robert[3], K. M. Kerr[4], S. Peters[5], J. Larkin[6] & K. Jordan[7], on behalf of the ESMO Guidelines Committee*

POSITION ARTICLE AND GUIDELINES Open Access

Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group

I. Puzanov[1†], A. Diab[2†], K. Abdallah[3], C. O. Bingham III[4], C. Brogdon[5], R. Dadu[2], L. Hamad[1], S. Kim[2], M. E. Lacouture[6], N. R. LeBoeuf[7], D. Lenihan[8], C. Onofrei[9], V. Shannon[2], R. Sharma[1], A. W. Silk[12], D. Skondra[10], M. E. Suarez-Almazor[2], Y. Wang[2], K. Wiley[11], H. L. Kaufman[12†], M. S. Ernstoff[1*†] and on behalf of the Society for Immunotherapy of Cancer Toxicity Management Working Group

Puzanov *et al. Journal for ImmunoTherapy of Cancer* (2017) 5:95

The Oncologist®

Melanoma and Cutaneous Malignancies

Management of Treatment-Related Adverse Events with Agents Targeting the MAPK Pathway in Patients with Metastatic Melanoma

Adil Daud, Katy Tsai

The Oncologist 2017;22:1–11

Optimizing combination dabrafenib and trametinib therapy in BRAF mutation-positive advanced melanoma patients: Guidelines from Australian melanoma medical oncologists

Victoria ATKINSON,[1] Georgina V. LONG,[2] Alexander M. MENZIES,[2] Grant MCARTHUR,[3] Matteo S. CARLINO,[4] Michael MILLWARD,[5] Rachel ROBERTS-THOMSON,[6] Benjamin BRADY,[3] Richard KEFFORD,[7] Andrew HAYDON[8] and Jonathan CEBON[9]

Asia-Pacific Journal of Clinical Oncology 2016; 12(Suppl. 7): 5–

Management of BRAF and MEK inhibito toxicities in patients with metastatic melanoma

Sarah J. Welsh and Pippa G. Corrie

Ther Adv Med Oncol

2015, Vol. 7(2) 122–136

Cutaneous adverse effects of targeted therapies

Part II: Inhibitors of intracellular molecular signaling pathways

James B. Macdonald, MD,[a,b] Brooke Macdonald, BA,[c] Loren E. Golitz, MD,[d,e]

J Am Acad Dermatol
February 2015

General management principles

Targeted therapy

Grade 1: continue TT, symptomatic therapy, diagnostic work-up

Grade 2:

- Interruption of treatment, until grade 1, then reintroduce in decreased dose
- If reappear, second interruption until grade 1 than reintroduce with further dose reduction
- Diagnostic work-up
- Symptomatic therapy

Grade 3 and 4

- Interruption of treatment until grade 1, then reintroduce in decreased dose
- Diagnostic work-up
- Symptomatic therapy
- Consider switching to other BRAFi+MEKi

Dose reductions for BRAFi MEKi

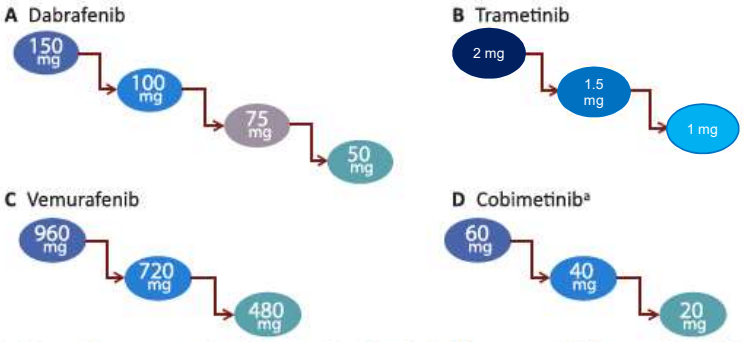


Figure 1. Recommended dose adjustments and modifications for dabrafenib **(A)**, trametinib **(B)**, vemurafenib **(C)**, and cobimetinib **(D)**.

General management principles

Immunotherapy

Grade 1: continue ICI therapy, symptomatic therapy, close follow-up

Grade 2:

- hold ICI therapy
- diagnostic work-up
- start corticosteroid therapy and resume ICI when corticosteroid is tapered to ≤10 mg/day and patient remains symptom-free (grade 1)
- If irAE returns on resuming ICI:
  - Grade ≤ 2: temporarily hold ICI
  - Grade ≥ 3: permanently discontinue ICI
- If using combination anti-CTLA-4/anti-PD-1 immunotherapy, continue anti-PD-1 agent only

Grade 3:

- withhold ICI; consider resuming ICI when
- corticosteroid is tapered to ≤10 mg/day and patient remains symptom-free (grade ≤ 1)
- If irAE returns: permanently discontinue ICI
- consider hospitalization

Grade 4: permanently discontinue ICI and hospitalize

Corticosteroid use for irAE

Grade of immune-related AE (CTCAE/equivalent)	Corticosteroid management	Additional notes
1	• Corticosteroids not usually indicated	• Continue immunotherapy
2	• If indicated, start oral prednisone 0.5-1 mg/kg/day if patient can take oral medication. • If IV required, start methylprednisolone 0.5-1 mg/kg/day IV • If no improvement in 2–3 days, increase corticosteroid dose to 2 mg/kg/day • Once improved to ≤grade 1 AE, start 4–6 week steroid taper	• Hold immunotherapy during corticosteroid use • Continue immunotherapy once resolved to ≤grade 1 and off corticosteroids • Start proton pump inhibitor for GI prophylaxis
3	• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) • If no improvement in 2–3 days, add additional/alternative immune suppressant • Once improved to ≤ grade 1, start 4–6-week steroid taper • Provide supportive treatment as needed	• Hold immunotherapy; if symptoms do not improve in 4–6 weeks, discontinue immunotherapy • Consider intravenous corticosteroids • Start proton pump inhibitor for GI prophylaxis • Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)
4	• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) • If no improvement in 2–3 days, add additional/alternative immune suppressant, e.g., infliximab • Provide supportive care as needed	• Discontinue immunotherapy • Continue intravenous corticosteroids • Start proton pump inhibitor for GI prophylaxis • Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)

Note: For steroid-refractory cases and/or when steroid sparing is desirable, management should be coordinated with disease specialists. AE, adverse event

Puzanov *et al. Journal for ImmunoTherapy of Cancer* (2017) 5:95

Dermatologic toxicities

Targeted therapy

Targeted therapy:

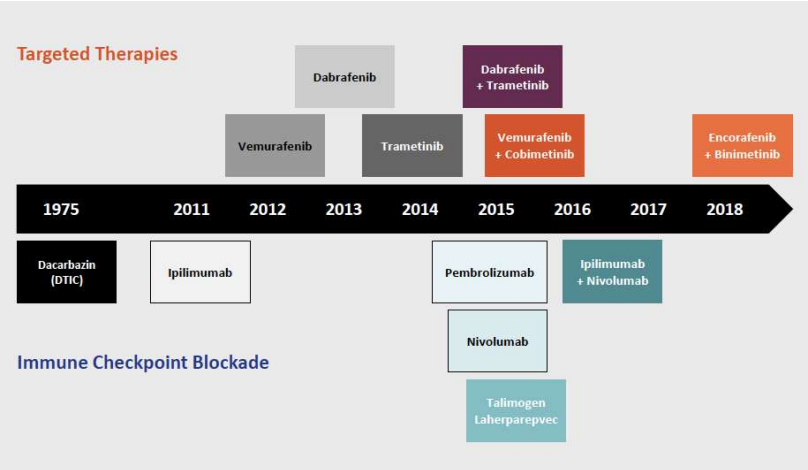
- BRAFi
  - Follicular rash
  - Maculopapular rash
  - Hair thinning and curling
  - cuSCC
  - Palmar-plantar dysestesia syndrome
- MEKi
  - Papulopustular rash
  - Palmar-plantar dysestesia syndrome

Immunotherapy

- Checkpoint inhibitor therapy
  - Pruritus
  - Maculopapular rash
  - Vitiligo
  - Rare
    - Neutrophilic dermatoses
    - Lichenoid reactions
    - Bullous pemphigoid
    - AGEP
    - Alopecia areata/universalis

TYPE > GRADE > MANAGEMENT

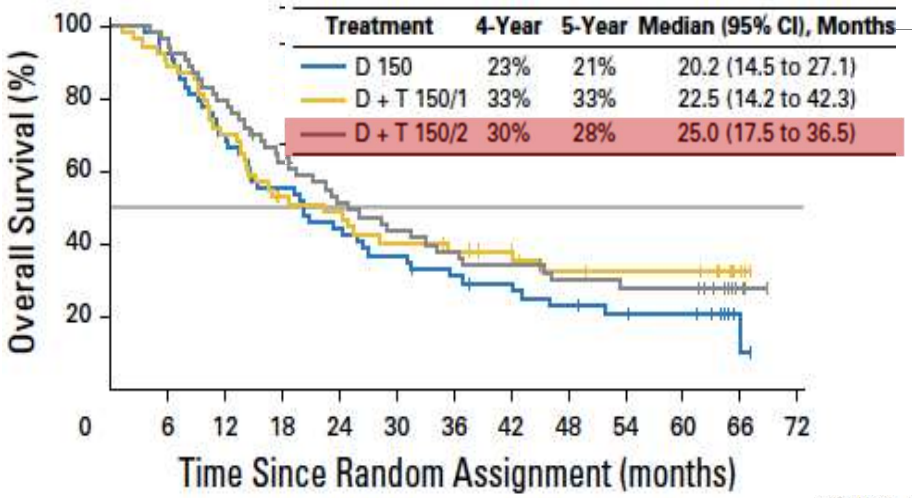
Melanoma 2020: standards of care and unmet needs



2020?

Hauschild A. EADO 2018

Dabrafenib trametinib 5-year OS update
(phase II, BRF113220, part C)

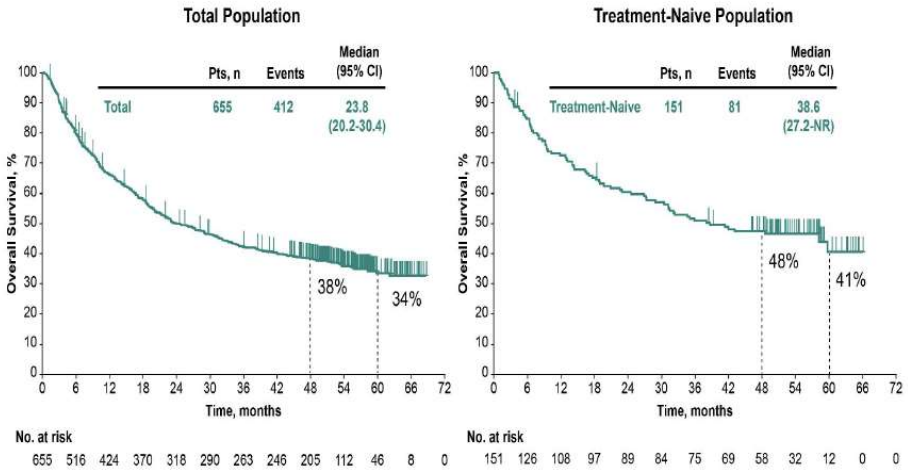


VOLUME 36 · NUMBER 7 · MARCH 1, 2018

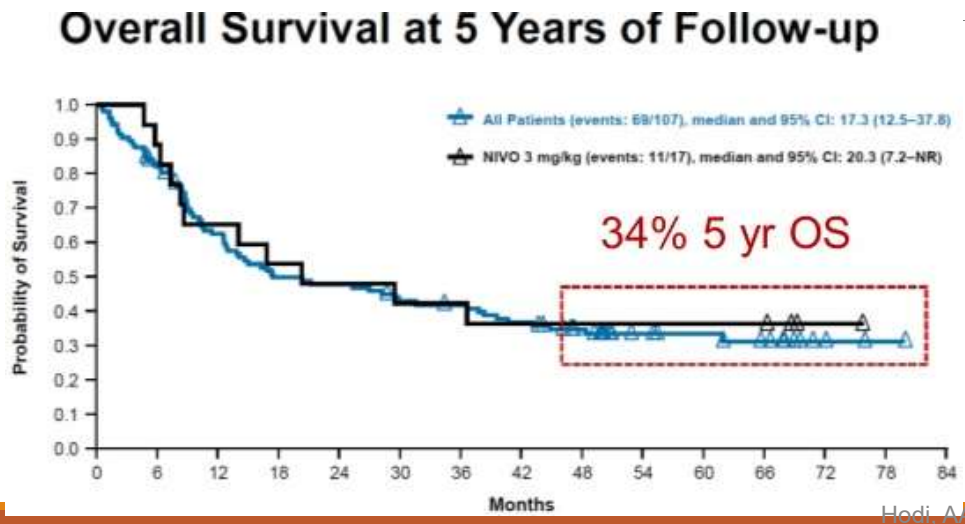
Long G et al. *J Clin Oncol 36:667-673.*

5-y-Overall Survival Pembro (KN-001 trial)

5-year survival:
Untreated pts 41%
Pre-treated and naive: 34%



Nivolumab: heavily pretreated patients



Hodi, AACR April, 2016

Metastatic melanoma treatment 2019

- Five year OS rates: 30-35%, 65-70% do not survive

Questions:

1. Duration of treatment?
2. Discontinuation of treatment?

Durable Complete Response After Discontinuation of Pembrolizumab in Patients With Metastatic Melanoma

Caroline Robert, Antoni Ribas, Omid Hamid, Adil Daud, Jedd D. Wolchok, Anthony M. Joshua, Wen-Jen Hwu, Jeffrey S. Weber, Tara C. Gangadhar, Richard W. Joseph, Roxana Dronca, Amita Patnaik, Hassane Zarour, Richard Kefford, Peter Hersey, Jin Zhang, James Anderson, Scott J. Diede, Scot Ebbinghaus, and F. Stephen Hodi

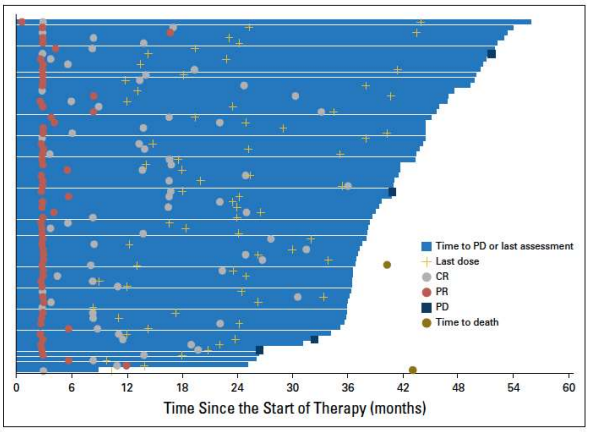


Fig 2. Time to response and durability of response from the start of therapy in complete responders who discontinued pembrolizumab and proceeded to observation (n = 67). Bar length is equivalent to the time to the last imaging assessment by investigator review. CR, complete response; PD, progressive disease; PR, partial response.

J Clin Oncol 36:1668-1674.

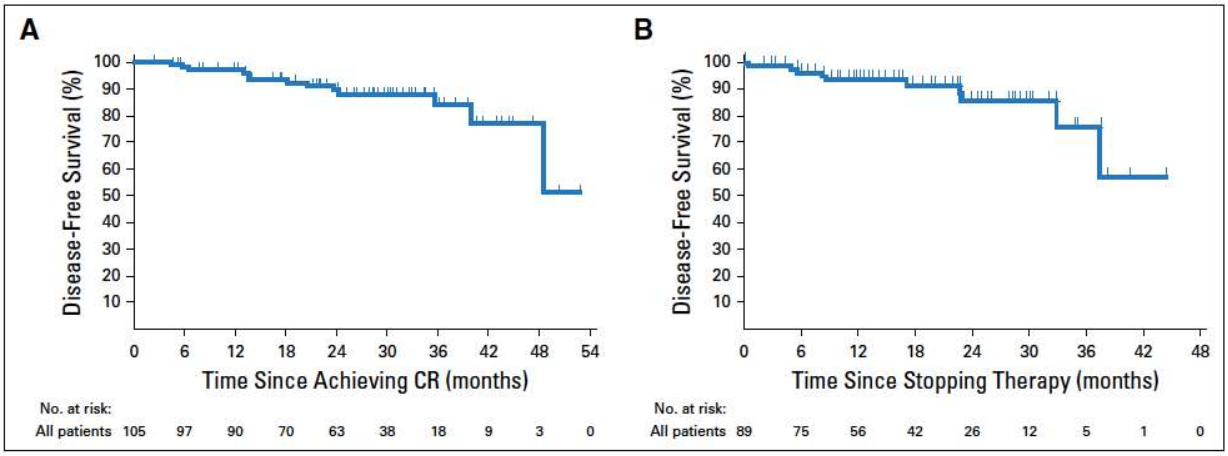


Fig 3. Disease-free survival (A) from time of experiencing complete response (CR) in all patients who achieved CR (n = 105) and (B) from time of discontinuation of pembrolizumab in patients who discontinued after CR for reasons other than progression (n = 89). The hash marks designate patients who were censored at that time point.

J Clin Oncol 36:1668-1674.

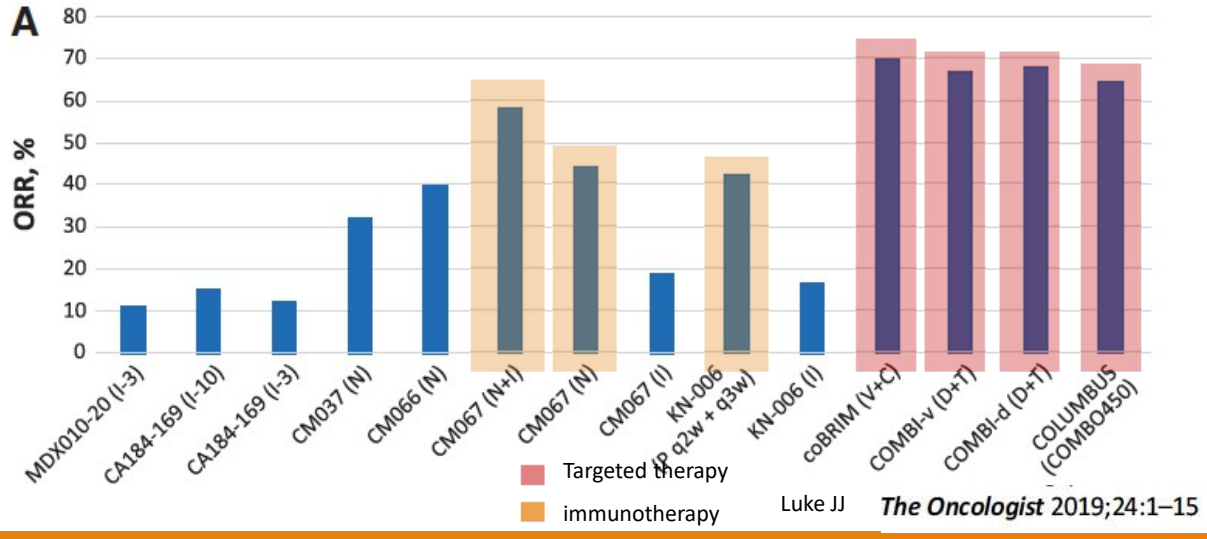
Metastatic melanoma treatment 2019

- Five year OS rates: 30-35%, 65-70% do not survive

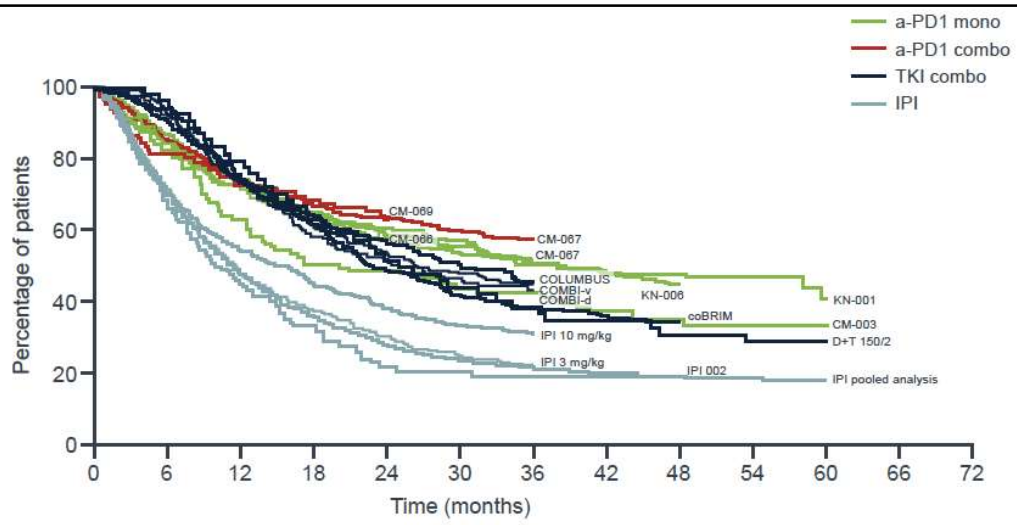
Questions:

1. Can we improve further treatment outcomes?
2. Are there evidence available to guide our treatment decision on choosing the first line treatment?
3. Does sequencing matters?

Metastatic melanoma: ORR



Luke JJ *The Oncologist* 2019;24:1–15



KN-006: Long GV et al. ASCO 2018; abstract 9503
KN-001: Hamid O et al. ASCO 2018; abstract 9516
CM-066: Atkinson V et al. SMR 2015
CM-003: Hodi FS et al. AACR 2016; abstract CT001
CM-067: Wolchok JD et al. N Engl J Med 2017; 377(14): 1345-56
CM-069: Hodi FS et al. Lancet Oncol 2016; 17(11): 1558-68
COLUMBUS: Dummer R et al. ASCO 2018; abstract 9504

D+T 150/2: Long GV et al. J Clin Oncol 2018; 36(7): 667-73
COMBI-d: Long GV et al. Ann Oncol 2017; 28(7): 1631-39
COMBI-v: Long GV et al. Ann Oncol 2016; 27(6): 1-36
coBRIM: Dreno B et al. ASCO 2018; abstract 9522
IPI 002: Hodi FS et al. N Engl J Med 2010; 363(8): 711-23
IPI pooled: Schadendorf D et al. J Clin Oncol 2015; 33(17): 1889-94
IPI 3/10mg: Ascierto PA et al. Lancet Oncol 2017; 18(5): 611-22

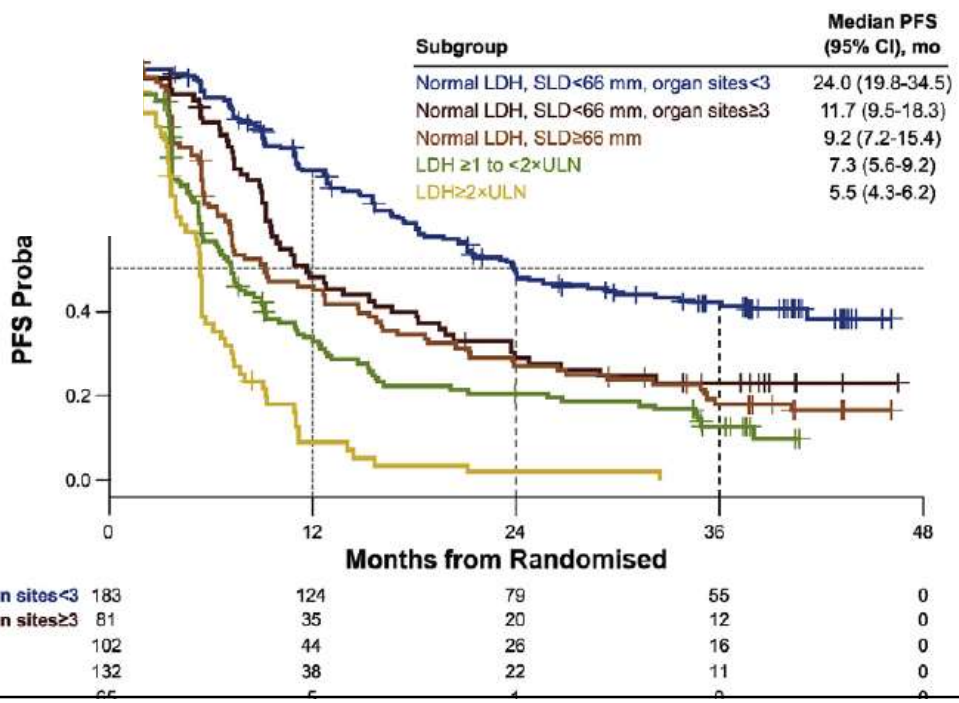
Important note: all curves are representative interpretations of source data from different studies. Curves from different studies cannot be compared directly.

OS rates: 1st line treatment

	3-year OS rate	4-year OS rate	5-year OS rate
Dabrafenib trametinib	45	37	34
Pembrolizumab	51	45	40
Nivolumab	51	45	-
Nivolumab+ipilimumab	58	52	-

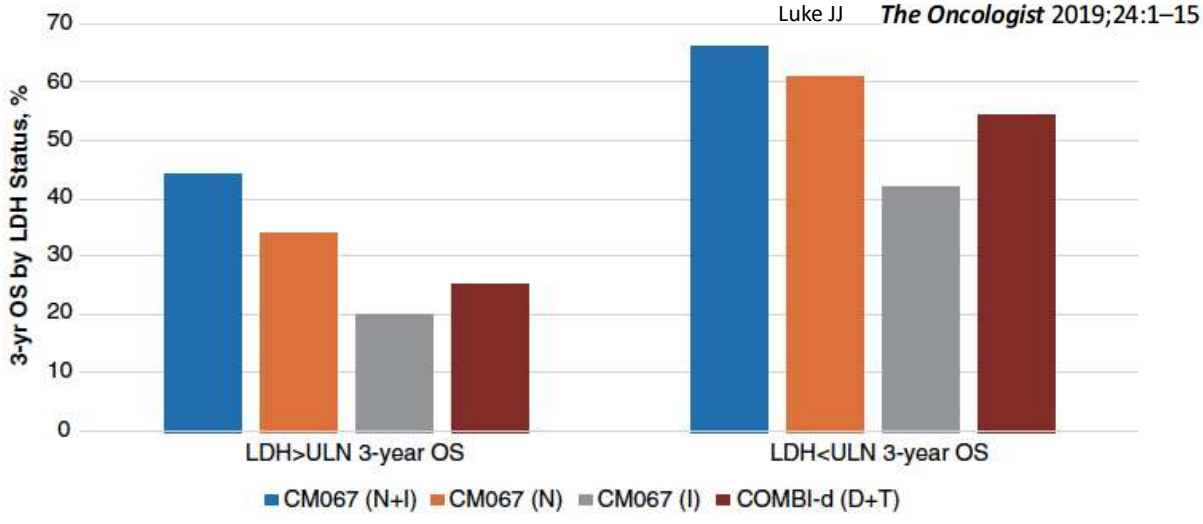
COMBI-D

Schadendorf D et al.
Eur J Cancer 2017



3-year OS and clinical factors

Luke JJ *The Oncologist* 2019;24:1–15



Sequencing and treatment outcome

- Only retrospective data available!
- Biased data due to the preference that for high tumor burden BRAFi+MEKi should be the 1st treatment option

Targeted agents or immuno-oncology therapies as first-line therapy for BRAF-mutated metastatic melanoma: a real-world study

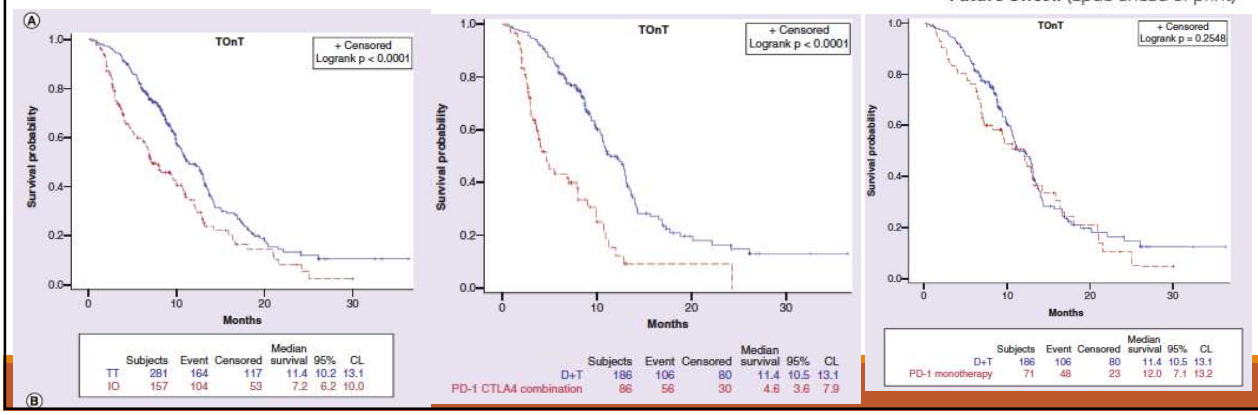
440 patients

IO-treated had a RECIST-determined response rate of 45.9 versus 60.1% for TT and time on treatment of 7.2 versus 11.4 months, respectively

There was no survivaldifference between cohorts (p = 0.664).

Luke JJ Feb2019

Future Oncol. (Epub ahead of print)



Comparative efficacy of combination immunotherapy and targeted therapy in the treatment of BRAF-mutant advanced melanoma: a matching-adjusted indirect comparison

Atkins et al.

Immunotherapy (2019) 11(7), 617–629

CheckMate 067† (N = 945) CheckMate 069† (N = 142) COMBI-d (N = 423) COMBI-v (N = 704) coBRIM (N = 495)

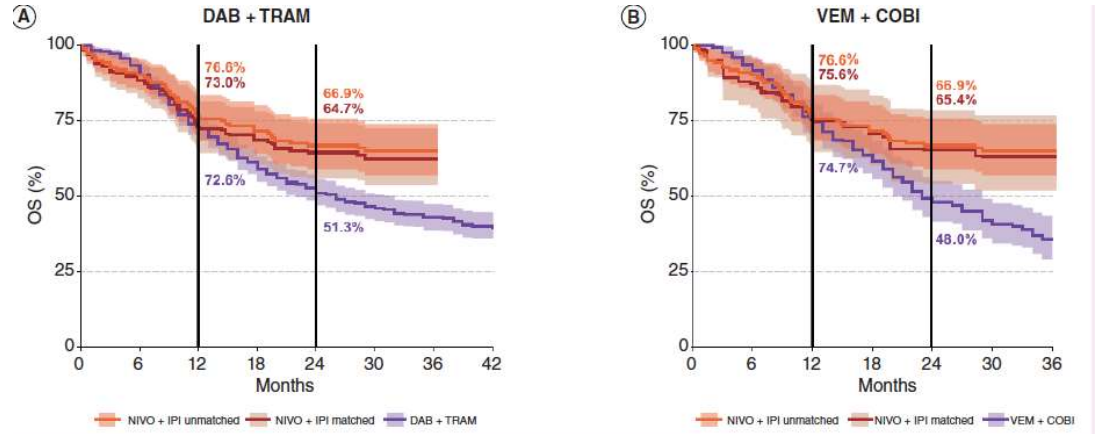


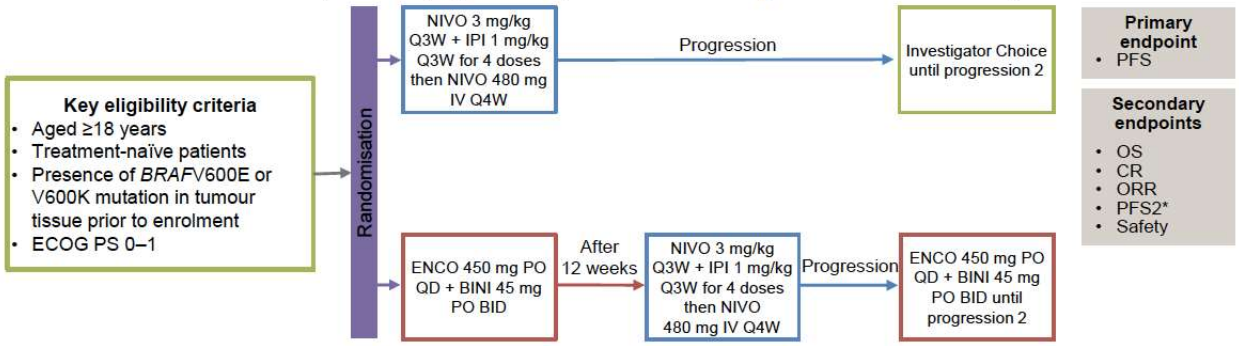
Figure 2. Overall survival comparisons. Comparison of OS before and after matching for nivolumab + ipilimumab versus dabrafenib + trametinib (A) and nivolumab + ipilimumab versus vemurafenib + cobimetinib (B).

Need for prospective data!

EORTC 1216: study design

Objective: to assess whether PFS can be improved with a sequential approach, using a 12-week induction of encorafenib + binimetinib, followed by combination nivolumab + ipilimumab, compared with nivolumab + ipilimumab alone, in patients with *BRAF*V600 mutation-positive unresectable or metastatic melanoma

Multicentre, two-arm, open-label, randomised comparative Phase 2 study



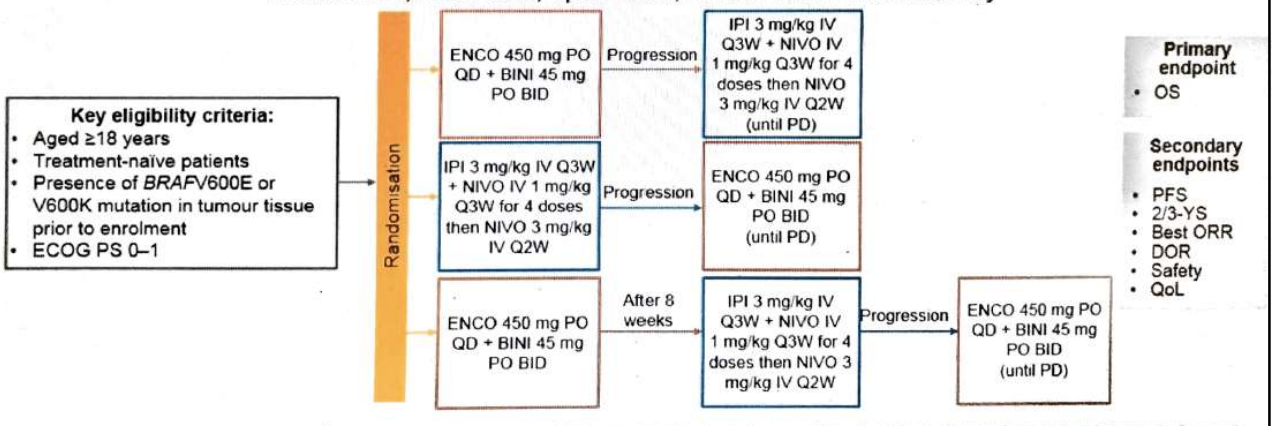
*PFS2 is defined as the time from randomisation to second objective disease progression, or death from any cause, whichever first

BID, twice daily; BINI, binimetinib; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ENCO, encorafenib; IPI, ipilimumab; IV, intravenous; NIVO, nivolumab; ORR, overall response rate; OS, overall survival;
PFS, progression-free survival; PO, orally; Q3W, every 3 weeks; Q4W, every 4 weeks; QD, once daily
ClinicalTrials.gov. NCT03235245. Available from: https://clinicaltrials.gov/(Accessed 15 October 2018)

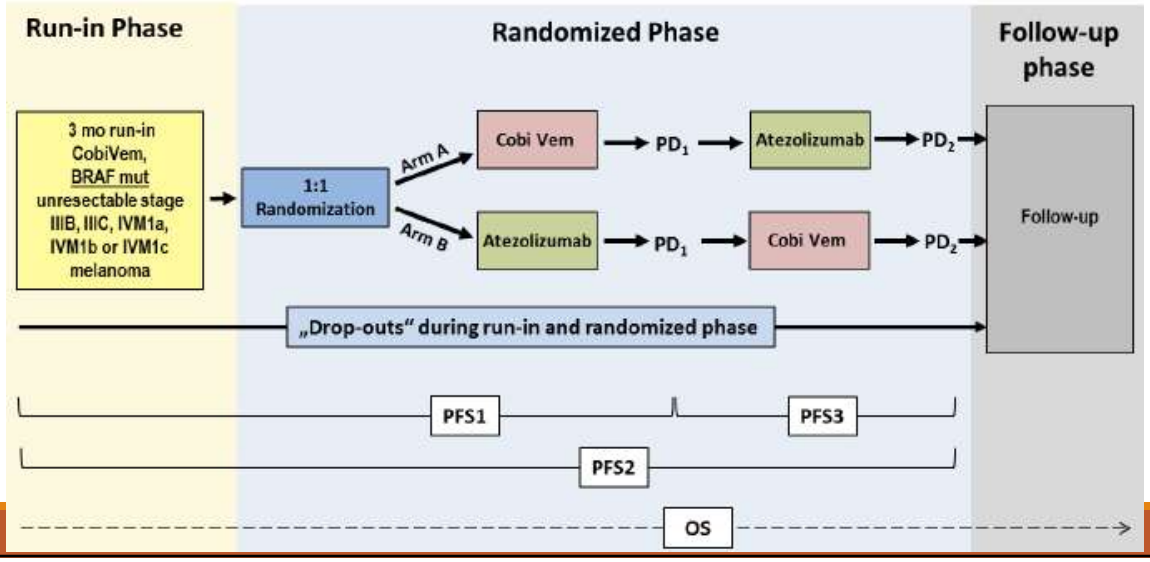
SECOMBIT: study design

Objective: to evaluate the best sequential approach with combination immunotherapy (ipilimumab + nivolumab) and combination target therapy (encorafenib + binimetinib) in patients with *BRAF*V600 mutation-positive unresectable or metastatic melanoma

Multicentre, three-arm, open-label, randomised Phase 2 study

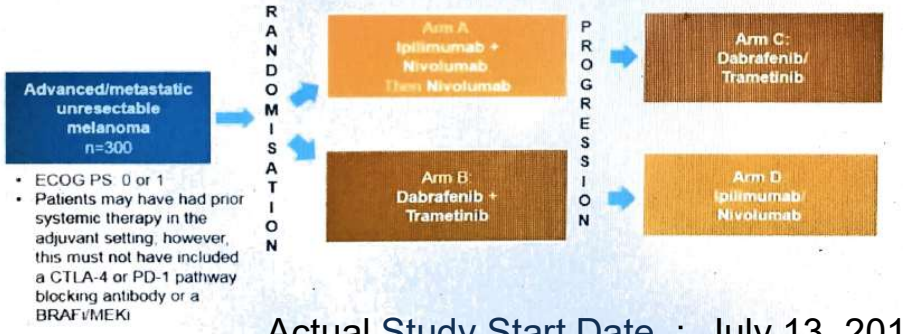


ImmunoCobiVem
(Germany, France, Greece, Serbia-VMA)



NCT02224781: Phase 3 Study of Dabrafenib + Trametinib Followed by Ipilimumab + Nivolumab vs Ipilimumab + Nivolumab Followed by Dabrafenib + Trametinib

Randomised Phase 3 trial of dabrafenib + trametinib followed by ipilimumab + nivolumab at progression vs ipilimumab + nivolumab followed by dabrafenib + trametinib at progression in patients with advanced BRAF V600 mutant melanoma



Primary endpoint:
- OS rate, defined as the proportion of patients alive after 2 years of follow-up time

Secondary endpoints:
- PFS (RECIST version 1.1)
- Response rate (RECIST version 1.1)

Objective:
Does the initial treatment with the dabrafenib-trametinib combination (and subsequent ipilimumab-nivolumab) or ipilimumab-nivolumab combination (and subsequent dabrafenib-trametinib combination) improve the 2-year OS significantly in patients with unresectable stage III or stage IV BRAFV600 mutant melanoma?

Actual Study Start Date : July 13, 2015

Estimated Primary Completion Date : October 2, 2022

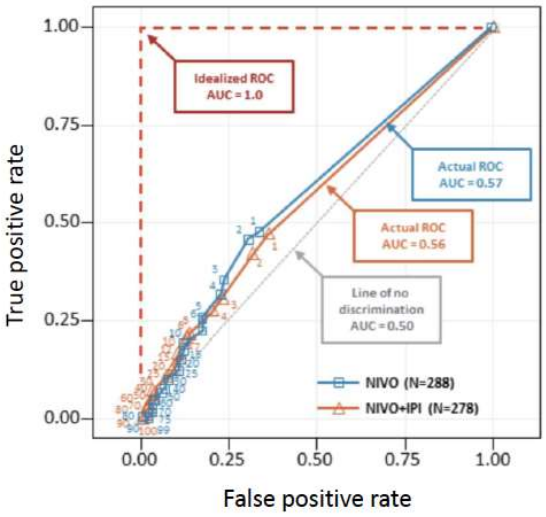
ECOG-PS: Eastern Cooperative Oncology Group performance status; OS: overall survival; PFS: progression-free

Predictive biomarkers?

No validated markers for IO in melanoma

- PD-L1: not standard of care
- MSI-high: not routine
- TMB mostly high in melanoma
- Main limitation:
  negative predictive value

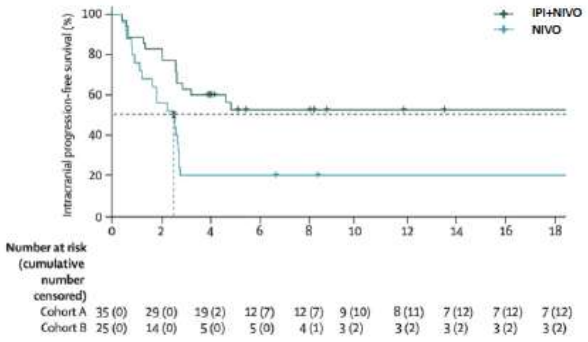
ROC curves confirm the poor performance of PD-L1 to guide patient selection: Fig. S4



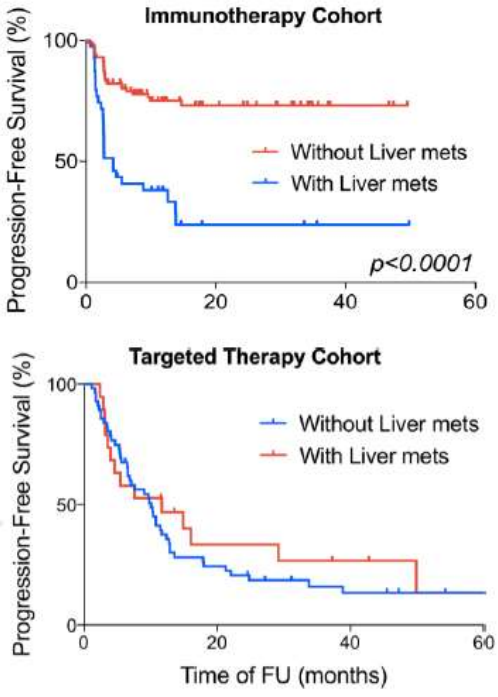
[1]Wolchok, *NEJM* 2017

Site of metastases

BRAIN METS

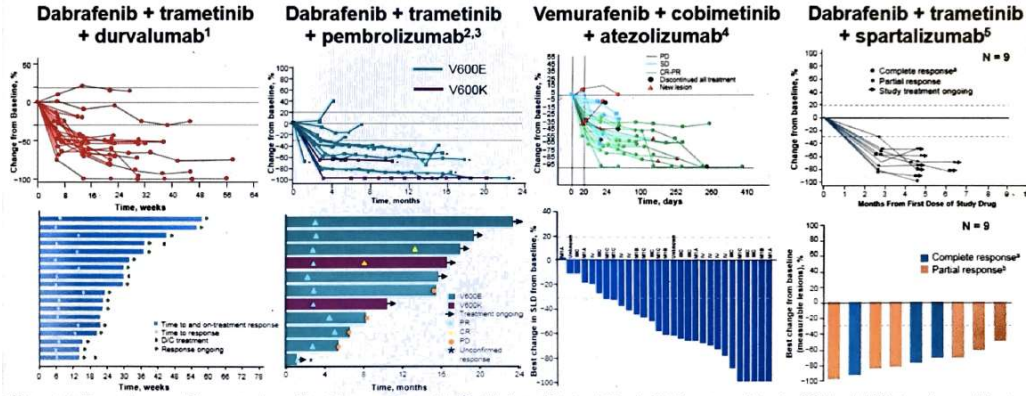


[1] Tawbi, *NEJM* 2018; [2] Long, *Lancet Oncol* 2018



Combination!

Clinical Trials Combining BRAFi + MEKi + anti–PD-1/L1



BID, twice daily; CR, complete response; PD, progressive disease; PR, partial response; QD, once daily; SD, stable disease. [a]Patients with CR and < 100% change in sum of diameters (SOD) have (a) 100% change for non-nodal target lesions and all nodal target lesions are < 10 mm and (b) CR for nontarget lesions. [b]Patients with PR and 100% change in SOD have (a) 100% change for all target lesions and (b) non-CR/non-PD response for nontarget lesions.

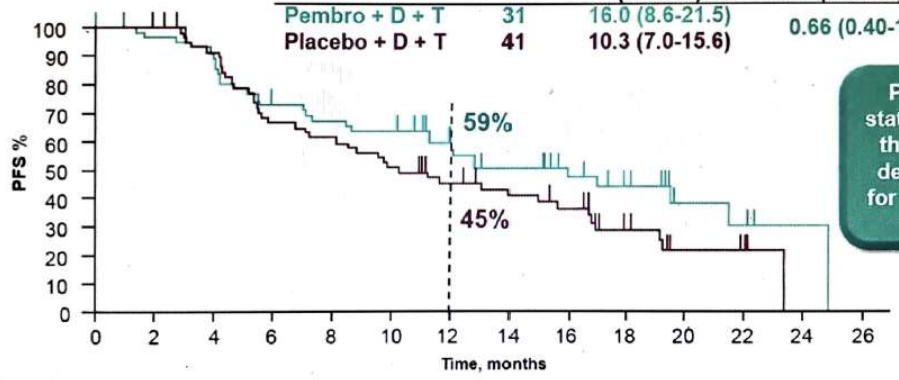
1. Ribas A, et al. *J Clin Oncol* 2015; 33(suppl) [abstract 3003]. 2. Ribas A, et al. *J Clin Oncol* 2016; 34(suppl) [abstract 3014]. 3. Ribas A, et al. *Ann Oncol* 2017; 28(suppl 5) [abstract 1216O]. 4. Hwu P, et al. *Ann Oncol* 2016; 27(suppl 6) [abstract 1109PD]. 5. Dummer R, et al. *J Clin Oncol* 2018;36(suppl 5S) [abstract 189].

PRESENTED BY R DUMMER AT AACR 2018

Courtesy of Dr Dummer

Progression-Free Survival

	Events, n	Median,[a] mo (95% CI)	HR[b] (95% CI)[b]	*P* Value[c]
Pembro + D + T	31	16.0 (8.6-21.5)	0.66 (0.40-1.07)	0.04287
Placebo + D + T	41	10.3 (7.0-15.6)		

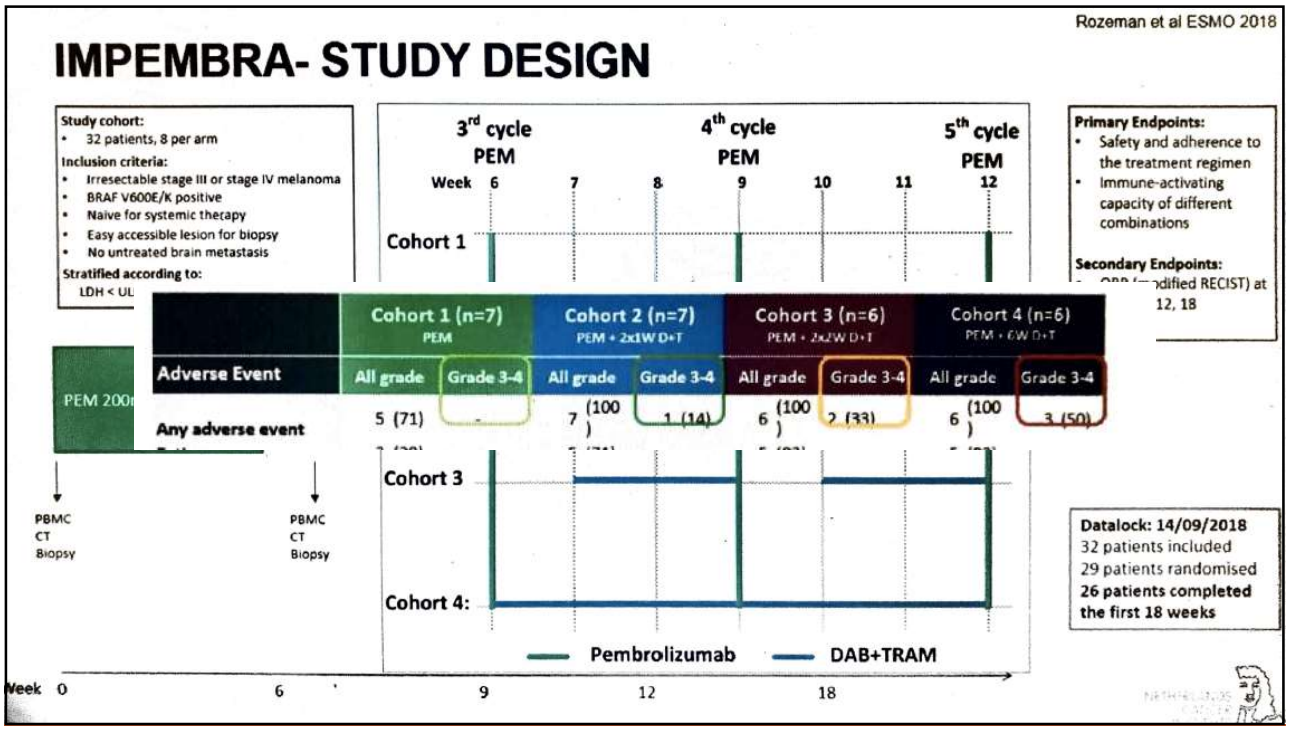


PFS did not reach statistical significance threshold per study design (required HR for significance ≤0.62, $P \leq 0.025$)

No. at risk

Pembro + D + T	60	55	49	39	36	34	27	21	17	12	5	4	1	0
Placebo + D + T	60	59	52	38	35	29	23	20	16	9	4	3	0	0

[a]Based on Kaplan-Meier estimate of PFS, per investigator assessment



Conclusion

- Long term follow up revealed similar rates of OS between targeted therapy and immunotherapy
- Prospective data are needed for a clear picture – trials underway
- What do we know? Not much…
  - In patients with liver metastases opt for targeted therapy first?
  - In patients with brain mets for the choice of immunotherapy opt for combination anti-CTLA4+anti-PD1
  - In high-volume disease: combination immunotherapy after debulking with BRAF+MEK?
  - Need for prospective data

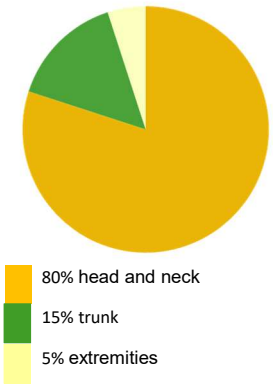
Systemic treatment of non-melanoma skin cancer

Janja Ocvirk
Institute of Oncology Ljubljana

Ljubljana, 5.9.2019

Basal cell carcinoma - BCC

- Basal cell carcinoma (BCC) grows from the basal layer of the epidermis and is the most commonly diagnosed malignant tumor and the most common form of skin cancer in the white population[1–4]
- The risk of occurrence of BCK in the white population is 30%[1,2]
- Poor reporting in registers
- The main cause of BCK is the exposure to UV radiation leading to cumulative DNA damage and gene mutations[1–5]



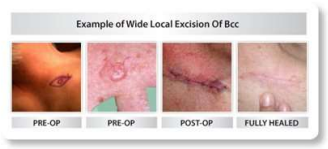
1. Rubin AI et al. N Engl J Med 2005;353:2262–9
2. Wong CSM et al. Br Med J 2003;327:794–8
3. Roewert-Huber J et al. Br J Dermatol 2007;157:47–51
4. Lear JT et al. J R Soc Med 1998;91:585–8
5. Caro I, Low JA. Clin Cancer Res 2010;16:3335–9

Treatment of basal cell carcinoma

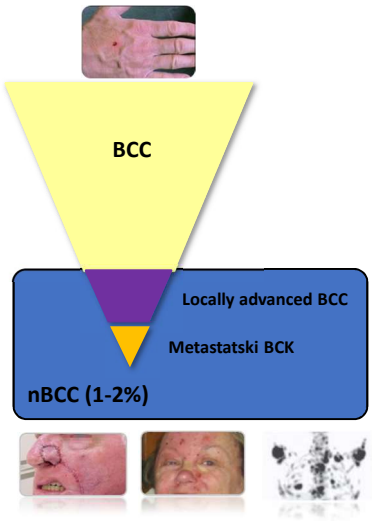
- Curettage and cavertisation, cryosurgery
- Imiquimod

- Surgical excision
- Electrochemotherapy
- Radiotherapy
- Targeted therapy -Vismodegib

nBCC

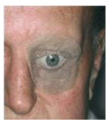


Advanced basal cell carcinoma



Locally advanced basal cell carcinoma (lnBCC)

Aggressive disease with local tissue damage
Frequent recurrences after surgery
The operation would cause deformation



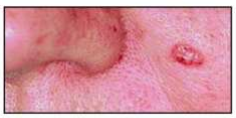
Metastatc BCC (mBCC)

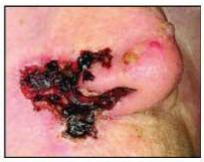
Rare but serious form of BCK
It involves the presence of metastases (e.g., lymph nodes, bones, lungs, liver [1]
Weak outcome (median survival: 8-14 months[2-3]
5-year survival rate: 10% [3,4]

1. Ting PT et al. J Cutan Med Surg 2005;9:10–15
2. von Domarus H, Stevens PJ. J Am Acad Dermatol 1984;10:1043–60
3. Lo JS et al. J Am Acad Dermatol 1991;24:715–19
4. Wong CSM et al. Br Med J 2003;327:794–8

Criteria for defining advanced form of BCC

- The lesion size ≥ 10 mm
- Growth of the tumor in the surrounding tissues and structures
- Surgical treatment / irradiation is contraindicated due to the position of the tumor or would lead to significant morbidity / deformation / loss of function
- Two or more repeated lesions in the same place [1]





1. Basset-Seguin N. et al. Mol Cancer Ther 2015; 1–9

BCC and Hedgehog signal pathway

- The pathway of cell growth and differentiation that controls the formation of organs in embryonic development
- The Hedgehog signaling pathway is inactive in most of the tissue of the adult
- Abnormal activation (mutation) of the Hedgehog signal pathway plays an important role in pathogenesis BCC[1]
- Hedgehog signaling pathway inhibitors provide a new treatment option for advanced patients BCC (vismodegib, sonidegib)

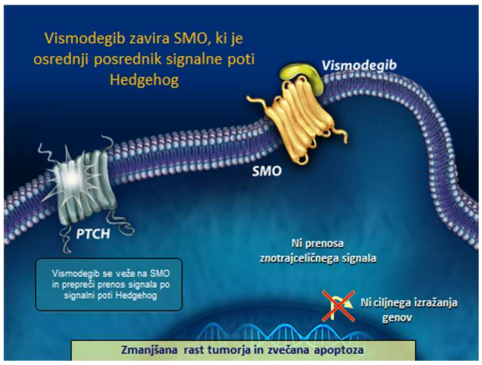


Table 1. Risk factors for recurrence[†].

	Clinical	Histological
Location	Low risk: trunk and limbs Intermediate risk: forehead, cheek, chin, scalp and neck High risk: nose and periorificial areas on the head and neck	Aggressive subtype[‡]: – Morpheaform – Infiltrating – Basosquamous – Multifocal
Size (largest tumor diameter)	>1 cm for high-risk location >2 cm for low- or intermediate-risk location	
Clinical aspect	Ill-defined lesions or morpheaform subtypes	
Disease status	Recurrent	

[†]Level of evidence 3 (i.e., based on case–control studies).
[‡]When several subtypes are associated, global prognosis depends on the component with the poorest prognosis.
Adapted with permission from [26].

Vismodegib in patients with advanced basal cell carcinoma (STEVIE): a pre-planned interim analysis of an international, open-label trial

Nicole Basset-Seguin, Axel Hauschild, Jean-Jacques Grob, Rainer Kunstfeld, Brigitte Dréno, Laurent Mortier, Paolo A Ascierto, Lisa Licitra, Caroline Dutriaux, Luc Thomas, Thomas Jouary, Nicolas Meyer, Bernard Guillot, Reinhard Dummer, Kate Fife, D Scott Ernst, Sarah Williams, Alberto Fittipaldo, Ioannis Xynos, Johan Hansson

Summary
Background The Hedgehog pathway inhibitor vismodegib has shown clinical benefit in patients with advanced basal Lancet Oncol 2015; 16: 729–36

	All patients (n=482*)	Patients with locally advanced basal cell carcinoma (n=453)	Patients with metastatic basal cell carcinoma (n=29)
Complete	155 (32%)	153 (34%)	2 (7%)
Partial	158 (33%)	149 (33%)	9 (31%)
Stable disease	128 (27%)	118 (26%)	10 (34%)
Progressive disease	15 (3%)	11 (2%)	4 (14%)
Missing/not evaluable	26 (5%)	22 (5%)	4 (14%)

Data are n (%). *Excludes patients without histologically confirmed disease (n=3) and without measurable disease (n=14).

Table 4: Best response to treatment

Vismodegib in patients with advanced basal cell carcinoma (STEVIE): a pre-planned interim analysis of an international, open-label trial

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Summary

Background The Hedgehog pathway inhibitor vismodegib has shown clinical benefit in patients with advanced basal

Lancet Oncol 2015; 16: 729–36

	All TEAEs		Grade 3–5 TEAEs	
	<12 months' exposure (n=314)	≥12 months' exposure (n=185)	<12 months' exposure (n=314)	≥12 months' exposure (n=185)
Any TEAE	307 (98%)	184 (99%)	130 (41%)	84 (45%)
Muscle spasms	169 (54%)	148 (80%)	21 (7%)	17 (9%)
Alopecia	154 (49%)	153 (83%)	1 (<1%)	1 (<1%)
Dysgeusia	139 (44%)	130 (70%)	8 (3%)	3 (2%)
Weight loss	80 (25%)	82 (44%)	4 (1%)	14 (8%)
Asthenia	76 (24%)	65 (35%)	9 (3%)	5 (3%)
Decreased appetite	74 (24%)	52 (28%)	7 (2%)	4 (2%)
Ageusia	75 (24%)	37 (20%)	6 (2%)	5 (3%)
Fatigue	50 (16%)	30 (16%)	9 (3%)	3 (2%)
Nausea	38 (12%)	42 (23%)	0	1 (<1%)
Diarrhoea	32 (10%)	51 (28%)	1 (<1%)	2 (1%)

Data are n (%). For the most common treatment-emergent adverse events (TEAEs) of any grade, event occurring in 10% or more of patients are reported. Events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version (version 4.0).

Table 3: Incidence of treatment-emergent adverse events according to duration of vismodegib exposure (≥12 months *vs* <12 months; n=499)

Vismodegib in patients with advanced basal cell carcinoma (STEVIE): a pre-planned interim analysis of an international, open-label trial

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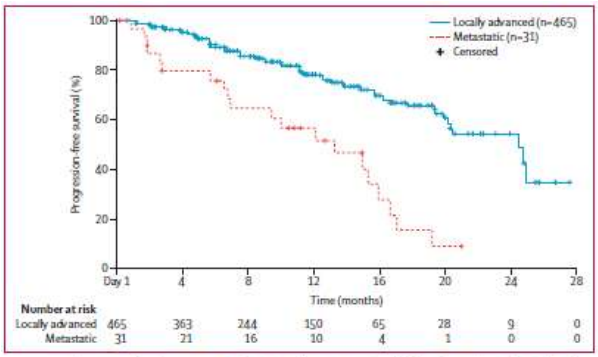
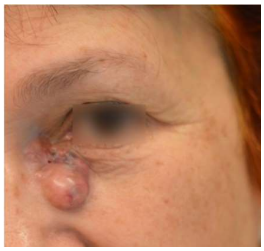


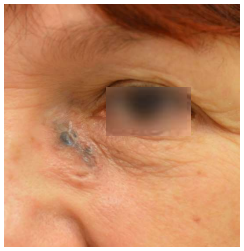
Figure 2: Kaplan-Meier plot of progression-free survival in patients who had histologically confirmed basal cell carcinoma

Case from OIL

23. 9. 2013



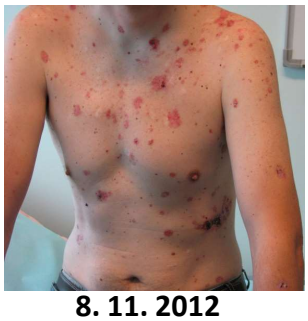
19. 12. 2013



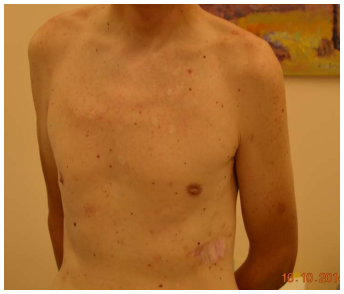
31. 7. 2014

Quick response to high-dose treatment
Side effects: alopecia gr. 2 after one year of treatment, increased CPK gr.1, muscle cramps gr.1

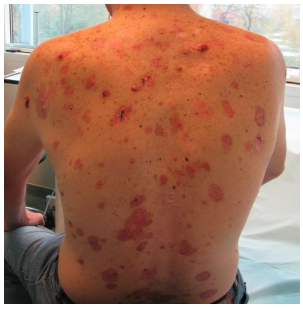
Case from OIL



Patient with Gorlin syndrome (multiple BCC)

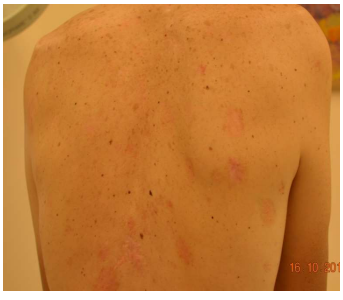


8. 11. 2012



Side effects: alopecia gr.1 weight loss gr.2 increased CPK gr.1-3

16. 10. 2014

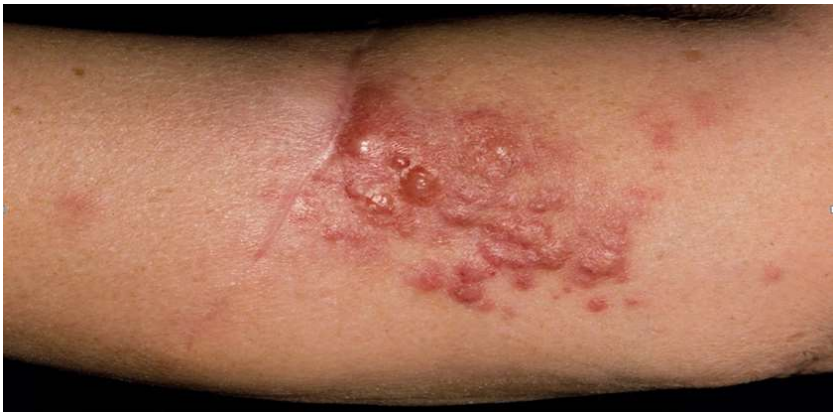


Merkel's cells carcinoma (MCC)

- MCC is a rare, aggressive and often deadly neuroendocrine skin cancer.
- Growing incidence (in the United States it tripled between 1986 and 2001).
- Possible connection with recently discovered polyomavirus (80% of MCC cells).
- It often occurs in the sun exposed areas of the skin.

There are two reasons for MCC

- Through onco- proteins encoded with the Merckel‘s Cell Polycom virus (MCPyV)
- The accumulation of mutations caused by UV radiation.
- More often in immunosuppressed patients



PRINCIPLES OF SYSTEMIC THERAPY[1]

Local Disease:
- Adjuvant chemotherapy not recommended

Regional Disease:
- Clinical trial (preferred)
- Adjuvant chemotherapy not routinely recommended as survival benefit has not been demonstrated in available retrospective studies, but could be used on a case-by-case basis if clinical judgement dictates
  - Cisplatin ± etoposide
  - Carboplatin ± etoposide

Disseminated Disease:
- Clinical trial (preferred)
- Avelumab[2]
- Pembrolizumab[2]
- Nivolumab[2]
- As clinical judgment dictates for patients with contraindications to checkpoint immunotherapy:
  - Cisplatin ± etoposide
  - Carboplatin ± etoposide
  - Topotecan
  - (CAV): Cyclophosphamide, doxorubicin (or epirubicin), and vincristine

[1] When available and clinically appropriate, enrollment in a clinical trial is recommended. The literature is not directive regarding the specific chemotherapeutic agent(s) offering superior outcomes, but the literature does provide evidence that Merkel cell carcinoma is chemosensitive, although the responses are not durable, and the agents listed above have been used with some success.

[2] Preliminary data from non-randomized trials in patients with MCC demonstrate that rates of durable response are improved with PD-1/PD-L1 blockade compared with cytotoxic therapy. The safety profiles for checkpoint immunotherapies are significantly different from cytotoxic therapies. Consult prescribing information for recommendations on detection and management of immune-related adverse events associated with checkpoint immunotherapies. Clinician and patient education is critical for safe administration of checkpoint immunotherapies.

Reason for use of immunotherapy in mMCC

- PD-L1 is expressed in MCC tumor cells and infiltrates of adjacent immune cells[1]
- Dysfunction of MCPyV-specific T cells[2]
  - -Levels of CD8 T cells increase with a higher tumor load
  - -Exhausted phenotype (PD-1 +, Tim-3 +)
- MCPyV-negative tumors have a higher burden on mutations and neoanthigens[3]

1. Lipson EJ, et al. *Cancer Immunol Res*. 2013;1(1):54-63; 2. Afanasiev O, et al. *Clin Cancer Res*. 2014;19(19):5351-60; 3. Goh G, et al. *Oncotarget*. 2016;7(3):3403-15.

Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial

Howard L Kaufman, Jeffery Russell, Omid Hamid, Shailender Bhatia, Patrick Terheyden, Sandra P D'Angelo, Kent C Shih, Céleste Lebbé, Gerald P Linette, Michele Milella, Isaac Brownell, Karl D Lewis, Jochem H Lorch, Kevin Chin, Lisa Mahnke, Anja von Heydebreck, Jean-Marie Grillerot, Paul Nghiem

- **88 patients were enrolled and received at least one dose of avelumab.**
- **Patients were followed up for a median of 10 · 4 months (IQR 8 · 6–13 · 1).**
- **The proportion of patients who achieved an objective response was 28 (31 · 8% [95 · 9% CI 21 · 9–43 · 1]) of 88 patients, including eight complete responses and 20 partial responses. Responses were ongoing in 23 (82%) of 28 patients at the time of analysis.**
- **Five grade 3 treatment-related adverse events occurred in four (5%) patients: lymphopenia in two patients, blood creatine phosphokinase increase in one patient, aminotransferase increase in one patient, and blood cholesterol increase in one patient; there were no treatment-related grade 4 adverse events or treatment-related deaths. Serious treatment-related adverse events were reported in fi ve patients (6%): enterocolitis, infusion-related reaction, aminotransferases increased, chondrocalcinosis, synovitis, and interstitial nephritis (n=1 each).**

Lancet Oncol 2016; 17: 1374–85

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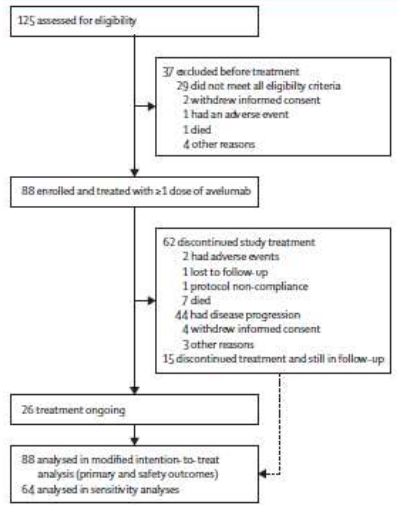

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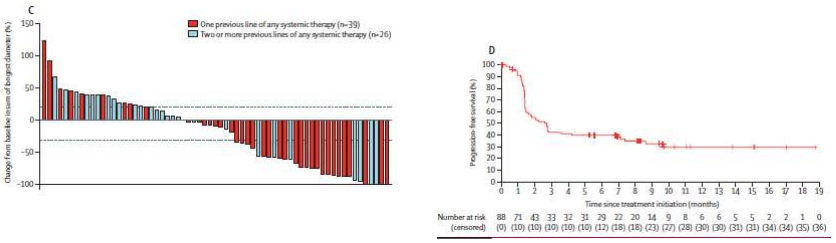


Lancet Oncol 2016; 17: 1374–85

	Grade 1-2	Grade 3
Fatigue	21 (24%)	0
Infusion-related reaction*	15 (17%)	0
Diarrhoea	8 (9%)	0
Nausea	8 (9%)	0
Asthenia	7 (8%)	0
Rash	6 (7%)	0
Decreased appetite	5 (6%)	0
Maculopapular rash	5 (6%)	0
Blood creatine phosphokinase increase	1 (1%)	1 (1%)
Lymphopenia	0	2 (2%)
Blood cholesterol increase	0	1 (1%)
Aminotransferase increase	0	1 (1%)
Potential immune-mediated treatment-related adverse event†		
Hypothyroidism	3 (3%)	0
Hyperthyroidism	2 (2%)	0
Pneumonitis	1 (1%)	0
Type 1 diabetes mellitus	1 (1%)	0

Any grade in at least 5% of patients or any grade 3 or worse adverse event based on the worst grade per patient; none were grade 4 or 5. The overall summary of safety is shown in the appendix (p 13), and tables listing all treatment-related adverse events occurring in more than one patient and all treatment-emergent adverse events regardless of causality occurring in at least 10% of patients are provided in the appendix (pp 14-19). *An infusion-related reaction in this analysis was based on a composite definition with five different Medical Dictionary for Regulatory Activities terms. Signs and symptoms of a potential infusion-related reaction (eg, fever, chills, or rigors) reported on the day of infusion (but not before dosing) or the following day were queried with investigators to ascertain whether an adverse event of "infusion-related reaction" should be recorded. Of the 15 treatment-related adverse events recorded as an infusion-related reaction, 13 (87%) of 15, resolved on the same day as the infusion. In one patient, resolution of a grade 1 event occurred within 3 days and without the use of concomitant corticosteroid, and in a second patient, a grade 2 event resolved within 6 days, also without the use of corticosteroid. Three patients received corticosteroid treatment for a grade 2 infusion-related reaction that resolved on the same day as the infusion. All other patients were treated with non-steroidal supportive medication. †These events were programmatically derived from a search term list. By manual medical review, potential immune-mediated, treatment-related adverse events were identified in four additional patients: grade 3 increased aminotransferase (n=1); grade 2 diarrhoea (n=1); grade 2 nephritis (n=1); and grade 1 rash (n=1).

Table 3: Treatment-related adverse events in the modified intention-to-treat population

- **Avelumab was associated with durable responses, most of which are still ongoing, and was well tolerated; hence, avelumab represents a new therapeutic option for advanced Merkel cell carcinoma.**

Lancet Oncol 2016; 17: 1374–85

Durable Tumor Regression and Overall Survival in Patients With Advanced Merkel Cell Carcinoma Receiving Pembrolizumab as First-Line Therapy

Paul Nghiem, MD, PhD[1]; Shailender Bhatia, MD[1]; Evan J. Lipson, MD[2]; William H. Sharfman, MD[2]; Ragini R. Kudchadkar, MD[3]; Andrew S. Brohl, MD[4]; Phillip A. Friedlander, MD[2]; Adil Daud, MD[2]; Harriet M. Kluger, MD[7]; Sunil A. Reddy, MD[8]; Brian C. Boulmay, MD[9]; Adam I. Riker, MD[9]; Melissa A. Burgess, MD[10]; Brent A. Hanks, MD, PhD[11]; Thomas Olencki, DO[12]; Kim Margolin, MD[13]; Lisa M. Lundgren, MS[14]; Abha Soni, DO[2]; Nirasha Ramchurren, PhD[14]; Candice Church, PhD[15]; Song Y. Park, MD[15]; Michi M. Shinohara, MD[15]; Bob Salim, PhD[16]; Janis M. Taube, MD[2]; Steven R. Bird, MS[17]; Nageatte Ibrahim, MD[17]; Steven P. Fling, PhD[14]; Blanca Homet Moreno, MD, PhD[17]; Elad Sharon, MD, MPH[18]; Martin A. Cheever, MD[14]; and Suzanne L. Topalian, MD[2]

In this multicenter phase II trial (Cancer Immunotherapy Trials Network-09/Keynote- 017), 50 adults naıve to systemic therapy for aMCC received pembrolizumab (2 mg/kg every 3 weeks) for up to 2 years. Radiographic responses were assessed centrally per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

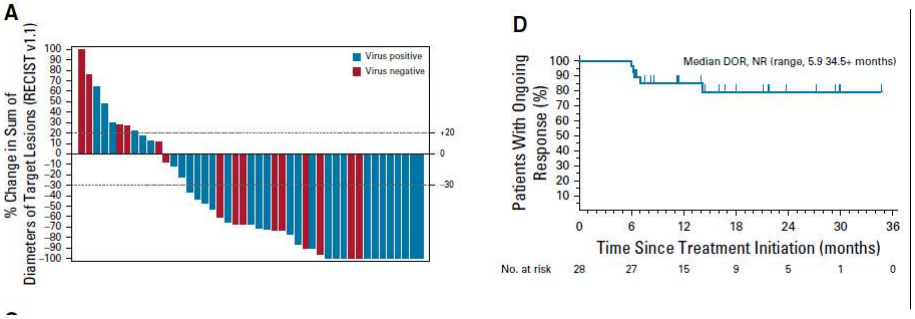
J Clin Oncol 37:693-702. 2019

- ORR to pembrolizumab was 56% (complete response [24%] plus partial response [32%]; 95% CI, 41.3% to 70.0%), with ORRs of 59% in virus-positive and 53% in virus-negative tumors.
- Median follow-up time was 14.9 months (range, 0.4 to 36.4+ months).
- Among 28 responders, median response duration was not reached (range, 5.9 to 34.5+ months).
- The 24-month PFS rate was 48.3%, and median PFS time was 16.8 months (95% CI, 4.6 months to not estimable).
- The 24-month OS rate was 68.7%, and median OS time was not reached.
- Although tumor viral status did not correlate with ORR, PFS, or OS, there was a trend toward improved PFS and OS in patients with programmed death ligand-1–positive tumors.
- Grade 3 or greater treatment-related adverse events occurred in 14 (28%) of 50 patients and led to treatment discontinuation in seven (14%) of 50 patients, including one treatment-related death.

J Clin Oncol 37:693-702. 2019

Durable Tumor Regression and Overall Survival in Patients With Advanced Merkel Cell Carcinoma Receiving Pembrolizumab as First-Line Therapy

Paul Nghiem, MD, PhD[1]; Shailender Bhatia, MD[1]; Evan J. Lipson, MD[2]; William H. Sharfman, MD[2]; Ragini R. Kudchadkar, MD[3]; Andrew S. Brohl, MD[4]; Phillip A. Friedlander, MD[5]; Adil Daud, MD[6]; Harriet M. Kluger, MD[7]; Sunil A. Reddy, MD[8]; Brian C. Boulmay, MD[9]; Adam I. Riker, MD[9]; Melissa A. Burgess, MD[10]; Brent A. Hanks, MD, PhD[11]; Thomas Olencki, DO[12]; Kim Margolin, MD[13]; Lisa M. Lundgren, MS[14]; Abha Soni, DO[2]; Nirasha Ramchurren, PhD[14]; Candice Church, PhD[15]; Song Y. Park, MD[15]; Michi M. Shinohara, MD[15]; Bob Salim, PhD[16]; Janis M. Taube, MD[2]; Steven R. Bird, MS[17]; Nageatte Ibrahim, MD[17]; Steven P. Fling, PhD[14]; Blanca Homet Moreno, MD, PhD[17]; Elad Sharon, MD, MPH[18]; Martin A. Cheever, MD[14]; and Suzanne L. Topalian, MD[2]



J Clin Oncol 37:693-702. 2019

In patients with aMCC receiving first-line anti–programmed cell death-1 therapy - Pembrolizumab demonstrated durable tumor control, a generally manageable safety profile, and favorable OS compared with historical data from patients treated with first-line chemotherapy.

J Clin Oncol 37:693-702. 2019

ONCOIMMUNOLOGY
2017, VOL. 0, NO. 0, e1338237 (13 pages)
https://doi.org/10.1080/2162402X.2017.1338237

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REVIEW

Immune evasion mechanisms and immune checkpoint inhibition in advanced merkel cell carcinoma

Dirk Schadendorf[a], Paul Nghiem[b], Shailender Bhatia[c], Axel Hauschild[d], Philippe Saiag[e], Lisa Mahnke[f], Subramanian Hariharan[g], and Howard L. Kaufman[h]

Table 2. Summary of data from trials of immunotherapy for the treatment of patients with advanced MCC.

Parameter	Pembrolizumab Study[7]	Avelumab Study[8]
Patient population	Treatment naive (first-line treatment)	Chemotherapy refractory (second-line or later treatment)
N	26 [a]	88
Primary end point	Objective response rate by RECIST v1.1	Confirmed best overall response by independent review committee per RECIST v1.1
Patient and disease characteristics		
Median age (range), years	68 (57–91)	73 (33–88)
Stage IIIB MCC, n (%)	2 (8)	0
Stage IV MCC, n (%)	24 (92)	88 (100)
Prior lines of systemic therapy, n (%)		
0	26 (100)	0
1	0	52 (59)
≥ 2	0	36 (41)
Median baseline extent of disease (range), mm	69 (13–182)	79 (16–404)
MCPyV-positive, n (%)	17 (65)	46 (52) [b]
Median duration of follow-up (range), months	7.6 (1.6–12.2)	10.4 (6–19)
Minimum duration of follow-up, months	1.6	6
Objective response rate		
Overall, % (95% CI)	56 (35–76)	32 (22–43) [c]
MCPyV-positive, % (n/N1) [d]	62 (10/16)	26 (12/46)
MCPyV-negative, % (n/N1)	44 (4/9)	36 (11/31)
Response durability		
Number of patients with ongoing response at data cutoff, % (n/N1)	86 (12/14)	82 (23/28)
Median duration of response (range), months [e]	Not reached (2+ to 10+)	Not reached (3+ to 18+)
Kaplan-Meier estimate of proportion of responses with ≥ 6 months' duration, % (95% CI)	Not reported	92 (70–98)
Durable response rate, % (95% CI) [f]	Not reported	29 (20–39) [e]
Progression-free survival		
Median, months (95% CI)	9 (5–not reached)	2.7 (1.4–6.9)
6-month rate, % (95% CI)	67 (49–86)	40 (29–5.0)
Overall survival		
Median, months (95% CI)	Not reported	11.3 (7.5–14.0)
6-month rate, % (95% CI)	Not reported	69 (58–78)
Treatment-related AE, n (%)		
Any grade	20 (77)	62 (70)
grade 3	2 (8)	4 (5)
grade 4	2 (8)	0 (0)

[a]25/26 patients had ≥ 1 tumor assessment during treatment.
[b]77/88 patients were evaluable for MCPyV status.
[c]A repeated CI for the ORR in the modified intent-to-treat analysis set (95.9% CI for the primary analysis) was calculated to account for the group sequential testing approach.
[d]N1, number evaluable.
[e]+ denotes a censored observation for durability of response.
[f]Durable response rate defined as the proportion of patients with a response of at least 6 months' duration and was estimated as the product of the objective response and the Kaplan-Meier estimate of 6 months' durability of response.

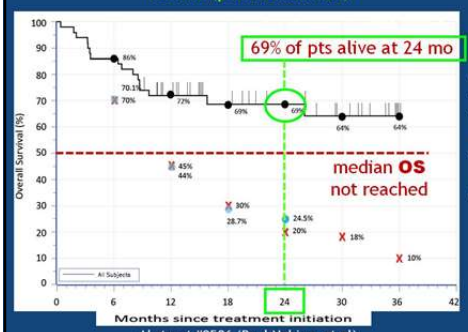
Immune Checkpoint Inhibition Trials in MCC: Advanced Metastatic Disease

Drug / Trial	Target	n	Prior chemo	Objective response	Median follow-up	Median PFS	Median OS
Pembrolizumab first-line[1] (NCT02267603) CITN-09	PD-1	26	No	56%	8 mo	Not reached	Not reached
Avelumab first-line[2] (NCT02155647) JAVELIN Merkel 200	PD-L1	29	No	63%	3 mo	Not reached	Not reached
Nivolumab first/second-line[3] (NCT02488759) CheckMate-358	PD-1	15 10	No Yes	73% 1st-L 50% 2nd-L	3+ mo	Not reached	Not reached
Avelumab second-line[4,5] (NCT02155647) JAVELIN Merkel 200	PD-L1	88	Yes	33%	16 mo	3 mo	13 mo

1. Nghiem PT *et al.*: *N Engl J Med* **374**:2542 (2016); 2. D'Angelo SP *et al.*: *ASCO* abstract 9530 (2017); 3. Topalian S *et al.*: *Cancer Res* **77**(13 Suppl): abstract CT074 (2017); 4. Kaufman HL *et al.*: *Lancet Oncol* **17**:1374 (2016); 5. Kaufman H et al.: J Immunother Cancer 6:7 (2018).

Anti-PD-1/PD-L1 in advanced MCC: first-line or second-line (chemo-naïve or chemo-pretreated) ?

1st line (pembrolizumab)



Abstract #9506 (Paul Nghiem et al)

2nd line (avelumab) after previous chemo

Abstract #9507 (Paul Nghiem et al)

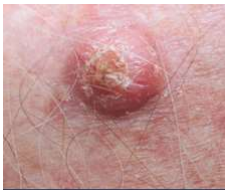
Anti PD-1/PD-L1 in advanced MCC

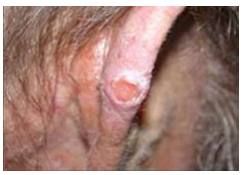
- **ORR** 1st line 56-73%
  2nd line 33-50%
- **PFS** 1st line 17 mo (median)
  2nd line 3 mo (median)
- **OS** 1st line median not reached
  2nd line 13 mo (median)

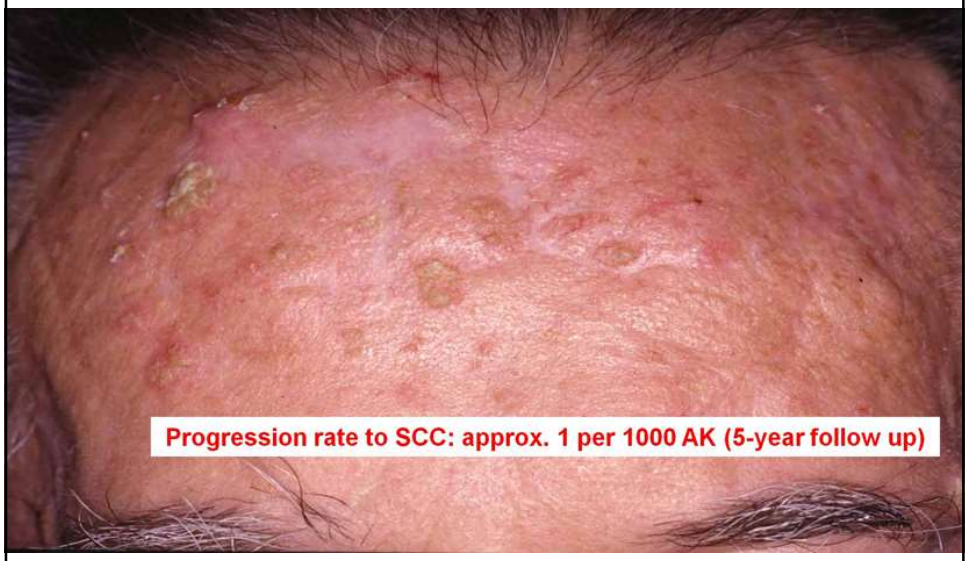
- Previous ChT impairs outcome of anti-PD-1/PD-L1
- anti-PD-1/PD-L1 should be applied as first-line treatment
- ChT should be postponed to 2nd line

SCC

- Second most common NMSC (20%)
- Incidence is rising in last 30 years (50-200%)
- Head and neck 80-90%
- 90% have good prognosis

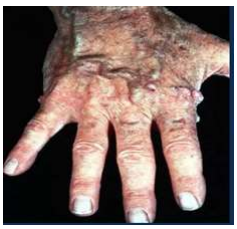
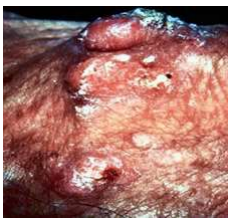
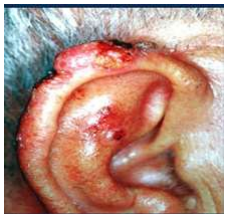






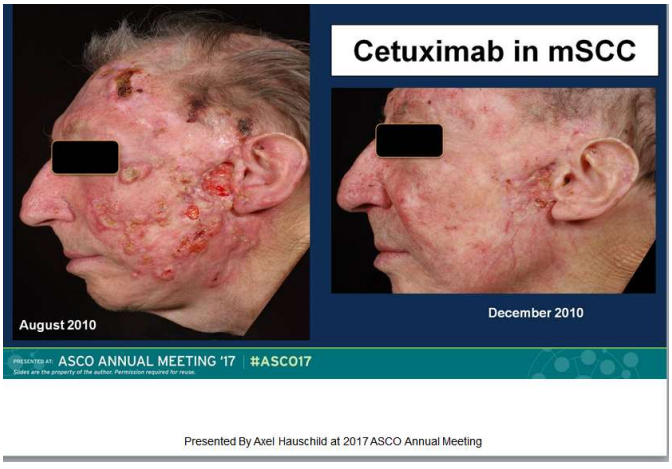
SCC in transplanted patients

36 x higher incidence than usual (BCC: SCC 4: 1)
Aggressive behavior - poor prognosis

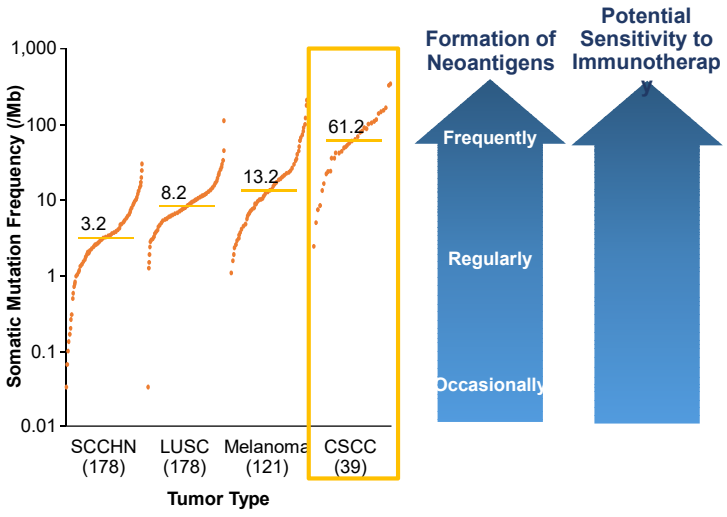
- Localized disease – surgery, electrochemotherapy
- Radiotherapy
- Advance disease - locally in systemic
- Pplatinum based chemotherapy – no standard schemas, shorter durance of remissions – 3 months
- Targeterd therapy: cetuximab (RR 21%), Panitumumab (31%)

NCCN Guidelines. V2.2018. https://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf.



Presented By Axel Hauschild at 2017 ASCO Annual Meeting

Tumor Mutational Burden in CSCC



Red horizontal line and associated number in figurer = median mutations per MB.
CSCC, cutaneous squamous cell carcinoma; LUSC, lung squamous cell carcinoma; Mb, megabase of DNA; SCCHN, Squamous cell carcinoma of the head and neck.
Pickering CR, et al. *Clin Cancer Res.* 2014;20:6582–6592.

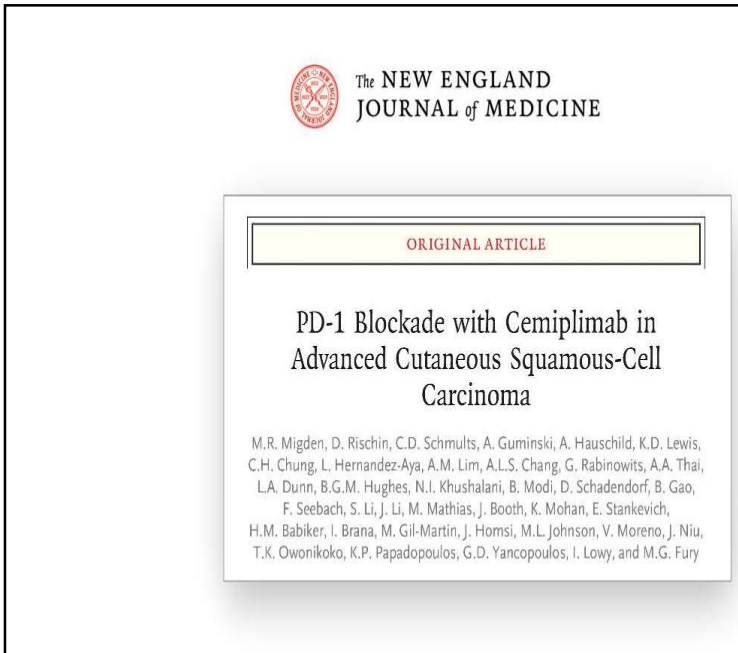
Rationale for Evaluating Checkpoint Inhibition in CSCC

- High tumor mutation burden (TMB) and immunogenic cancer
  - High TMB may contribute to increased neoantigen production, which may increase tumor antigenicity[1]
- Immunosuppression is a well-described risk factor for CSCC (especially in solid-organ transplant patients)[2]
- PD-L1 expression has been observed in advanced CSCC[3]

1. Pickering CR, et al. *Clin Cancer Res*. 2014;20:6582-92; 2. Euvrard E, et al. *N Engl J Med*. 2003;348:1681-1691.
3. Slater NA, et al. *J Cutan Pathol*. 2016;43:663-70.

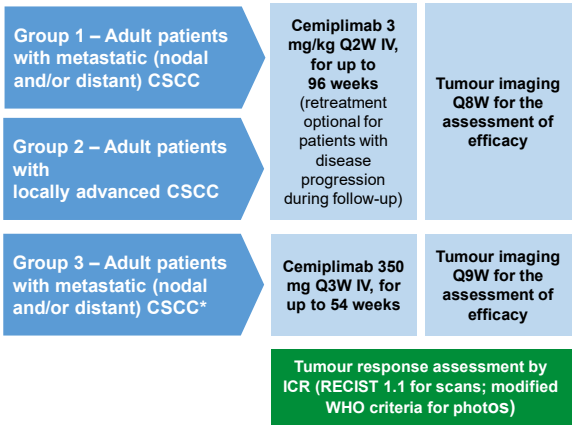
Candidates for Immunotherapy for Advanced CSCC

- Patients with advanced CSCC
  - Locally advanced / metastatic disease
- Patients who have failed prior surgeries
- Patients who are not surgical candidates due to morbidity / potential disfigurement or low confidence of clear margins
- Patients not candidates for radiotherapy



Migden MR, et al. *N Engl J Med*. 2018;379:341-351.

EMPOWER-CSCC-1 Study Design (NCT02760498)



Key inclusion criteria
- ECOG performance status of 0 or 1
- Adequate organ function
- Groups 1 & 3:
  - At least one lesion measurable by RECIST 1.1
- Group 2:
  - At least one lesion measurable lesion by RECIST 1.1 criteria (for scans) or modified WHO criteria (for photos)
  - CSCC lesion that is not amenable to surgery or radiotherapy per investigator assessment

Key exclusion criteria
- Ongoing or recent (within 5 years) autoimmune disease requiring systemic immunosuppression
- Prior anti–PD-1 or anti–PD-L1 therapy
- History of solid organ transplant, concurrent malignancies (unless indolent or not considered life threatening; for example, basal cell carcinoma), or haematologic malignancies

*Data not yet available
CSCC, cutaneous squamous cell carcinoma; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; PD, programmed cell death; PD-L, PD-ligand; Q[n]W, every [n] weeks; RECIST 1.1, Response Evaluation Criteria In Solid Tumours version 1.1; WHO, World Health Organisation.

1. Guminski et al. *J Clin Oncol.* 2019:37 (suppl; abstr 9526) [poster presentation]. 2. Migden MR, et al. *J Clin Oncol.* 2019:37 (suppl; abstr 6015) [poster presentation].

Group 1: Data cut-off date: September 20, 2018
Group 2: Data cut-off date: October 10, 2018

Baseline Characteristics in EMPOWER-CSCC-1 with Advanced CSCC (Group 1 and Group 2)

	Metastatic CSCC (N=59)[1]	Locally advanced CSCC (N=78)[2]
Median age, years (range)	71 (38–93)	74 (45–96)
≥ 65 years, n (%)	43 (72.9)	59 (75.6)
Male sex, n (%)	54 (91.5)	59 (75.6)
ECOG performance status, n (%)		
0 / 1	23 (39.0) / 36 (61.0)	38 (48.7) / 40 (51.3)
Primary CSCC site, n (%)		
Head/neck	38 (64.4)	62 (79.5)
Extremity	12 (20.3)	14 (17.9)
Trunk	9 (15.3)	2 (2.6)
Prior systemic therapy for CSCC, n (%)		
Any	33 (55.9)	12 (15.4)
1	22 (37.3)	10 (12.8)
≥2	11 (18.6)	2 (2.6)
Prior radiotherapy for CSCC, n (%)	50 (84.7)	43 (55.1)
Median duration of follow-up, months (range)	16.5 (1.1–26.6)	9.3 (0.8–27.9)

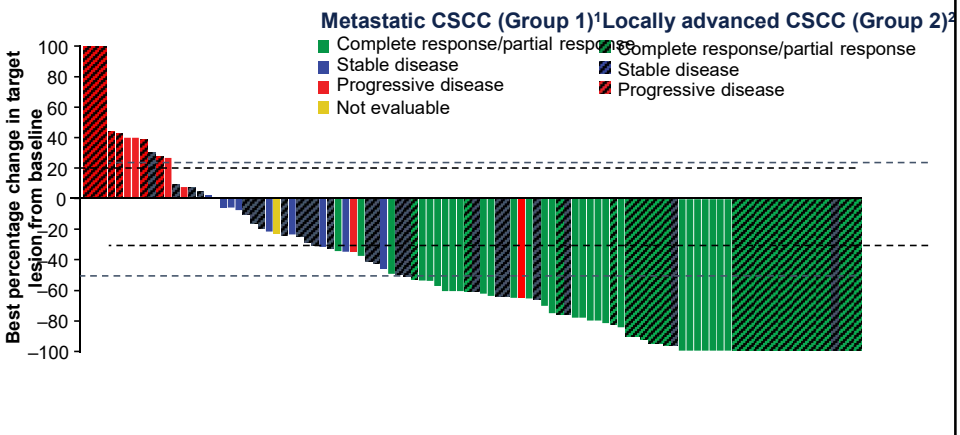
Data cut-off date: Sept 20, 2018 (Group 1)1; Oct 10, 2018 (Group 2)
CSCC, cutaneous squamous cell carcinoma; ECOG PS, Eastern Cooperative Oncology Group
†excludes ear and temple ‡ includes arms/hands and legs/feet
1. Guminski et al. *J Clin Oncol.* 2019:37 (suppl; abstr 9526) [poster presentation]. 2. Migden MR, et al. *J Clin Oncol.* 2019:37 (suppl; abstr 6015) [poster presentation].

Tumor Response Assessment by Independent Central Review in Patients with Advanced CSCC (Group 1 and 2)

	Metastatic CSCC (N=59)[1]	Locally Advanced CSCC (N=78)[2]
Median duration of follow-up, months (range)	16.5 (1.1 – 26.6)	9.3 (0.8 – 27.9)
Best overall response, n (%)		
Complete Response (CR)	10 (16.9)	10 (12.8)
Partial Response	19 (32.2)	24 (30.8)
Stable Disease	9 (15.3)	28 (35.9)
Non-CR/non-PD†	4 (6.8)	0
Progressive Disease (PD)	10 (16.9)	9 (11.5)
Not evaluable‡	7 (11.9)	7 (9.0)
Objective response rate (ORR), % (95% CI)	49.2 (35.9–62.5)	43.6 (32.4–55.3)
ORR by INV % (95% CI)	49.2 (35.9-62.6)	52.6 (40.9-64.0)
Complete Response / Partial Response	4 (6.8) / 25 (42.3)	13 (16.7) / 28 (35.9)
Disease control rate, % (95% CI)	71.2 (57.9–82.2)	79.5 (68.8–87.8)
Durable disease control rate, % (95% CI)§	62.7 (49.1–75.0)	62.8 (51.1–73.5)
Median observed time to response, months (range)¶	1.9 (1.7–9.1)	1.9 (1.8–8.8)

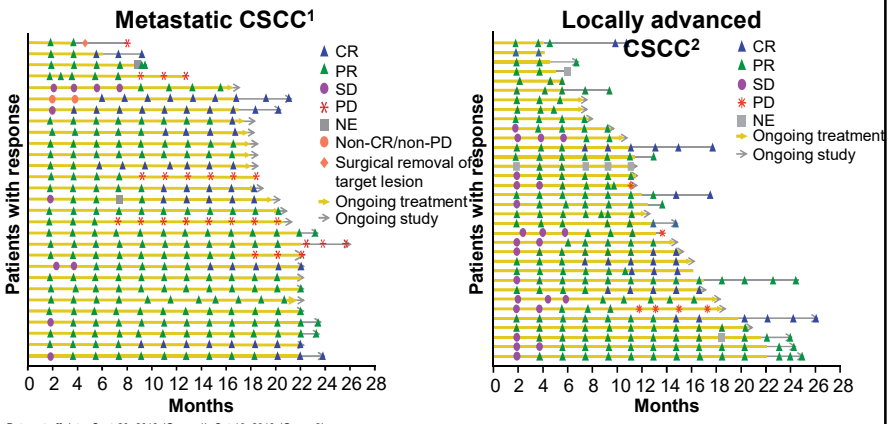
Data cut-off date: Sept 20, 2018 (Group 1); Oct 10, 2018 (Group 2)
†Patients with non-measurable disease on central review of baseline imaging. ‡Include missing and unknown tumor response. §Defined as the proportion of patients without progressive disease for at least 105 days. ¶Data shown are from patients with confirmed responses.
INV investigator assessment
1. Guminski et al. *J Clin Oncol.* 2019;37 (suppl; abstr 9526) [poster presentation]. 2. Migden MR, et al. *J Clin Oncol.* 2019;37 (suppl; abstr 6015) [poster presentation].

Best Percentage Change in Target Lesion in Patients with Advanced CSCC per ICR



Data cut-off date: Sept 20, 2018 (Group 1); Oct 10, 2018 (Group 2)
Bars show the best percentage change in the sum of target lesion diameters from baseline for 45 patients with metastatic CSCC who underwent radiologic evaluation per ICR and 56 patients with locally advanced CSCC who underwent photography evaluation per modified WHO criteria by ICR after treatment initiation. Lesion measurements after progression were excluded. Black horizontal dashed lines indicate RECIST 1.1 criteria for partial response (≥30% decrease in the sum of target lesion diameters) and progressive disease (≥20% increase in the target lesion diameters). Blue horizontal dashed lines indicate WHO criteria for partial response (≥50% decrease in the sum of target lesion diameters) and progressive disease (≥25% increase in the target lesion diameters).
CSCC, cutaneous squamous cell carcinoma; ICR, independent central review; RECIST 1.1, Response Evaluation Criteria In Solid Tumors version 1.1; WHO, World Health Organization
1. Guminski AD, et al. *J Clin Oncol* 2019;37 (suppl; abstr 9526); 2. Migden MR, et al. *J Clin Oncol* 2019;37 (suppl; abstr 6015)

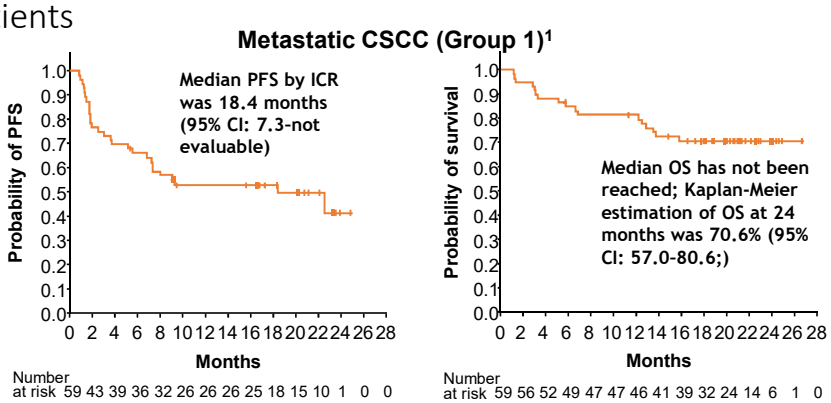
Time to Response and Duration of Response in the Responding Patients with Advanced CSCC



Data cut-off date: Sept 20, 2018 (Group 1); Oct 10, 2018 (Group 2)
†Twenty-three of the 29 patients remain in response at time of data cut-off; of the 23 patients, 10 were still on study, 11 were in post-treatment follow-up and two were off study. Multiple progression events for a single patient were possible due to discrepancies between investigator and ICR assessments of tumour response and because the protocol allowed option for treatment past progression in patients whom the investigator felt were experiencing clinical benefits. ‡Of the 34 responding patients, three had subsequent progressive disease. Among the remaining 31 patients who were in response at the time of data cut-off, 12 were still on study treatment, nine were in post-treatment follow-up, and 10 were off study. One patient (sixth from bottom) had four progressive disease assessments due to discordance between investigator and ICR assessments of tumour response.
CR, complete response; CSCC, cutaneous squamous cell carcinoma; ICR, independent central review; NE, not evaluable;
PD, progressive disease; PR, partial response; SD, stable disease.

1. Guminski et al. *J Clin Oncol.* 2019:37 (suppl; abstr 9526) [poster presentation]. 2. Migden MR, et al. *J Clin Oncol.* 2019:37 (suppl; abstr 6015) [poster presentation].

Kaplan–Meier Estimation Overall Survival, Progression-Free Survival, and Duration of Response in Advanced CSCC Patients



Median DOR not reached

	Locally Advanced CSCC (Group 2)[2]
Median PFS	NR
K-M Estimated PFS at 12 months	58.1% (95% CI: 43.7–70.0)
Median OS	NR
K-M Estimated OS at 12 months	93.2% (95% CI: 84.4–97.1)
Median DOR	NR

Group 1: Median duration of follow-up = 16.5 mos (range 1.1 – 26.6); Group 2: Median duration of follow-up = 9.3 mos (range 0.8 – 27.9)
Data cut-off date: Sept 20, 2018 (Group 1); Oct 10, 2018 (Group 2)
CI, confidence interval; CSCC, cutaneous squamous cell carcinoma; ICR, independent central review; OS, overall survival; PFS, progression-free survival;
NR, not reached

1. Guminski et al. J Clin Oncol. 2019:37 (suppl; abstr 9526) [poster presentation]. 2. Migden MR, et al. J Clin Oncol. 2019:37 (suppl; abstr 6015) [poster presentation].

Treatment-emergent Adverse Events (TEAEs), Regardless of Attribution, in Patients with Advanced CSCC

	Group 1 Metastatic CSCC (N=59)[1]		Group 2 Locally advanced CSCC (N=78)[2]		Overall (N=137)[3]	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any	59 (100.0)	30 (50.8)	78 (100.0)	34 (43.6)	137 (100.0)	64 (46.7)
Serious	24 (40.7)	20 (33.9)	23 (29.5)	19 (24.4)	47 (34.3)	39 (28.5)
Led to discontinuation	6 (10.2)	4 (6.8)	6 (7.7)	5 (6.4)	12 (8.8)	9 (6.6)

Metastatic CSCC (Group 1)[1]

Grade ≥3 TEAEs occurring in >1 patient
- Cellulitis (n=4; 6.8%)
- Pneumonitis (n=3; 5.1%)
- Anemia, dyspnea, hypercalcemia, new primary CSCC, pleural effusion, and pneumonia (each n=2; 3.4%)

Grade ≥3 TEAEs leading to treatment discontinuation
- Pneumonitis (n=3; 5.1%)
- Aseptic meningitis, confusional state, and neck pain (all in the same patient: n=1; 1.7%)

Locally advanced CSCC (Group 2)[2]

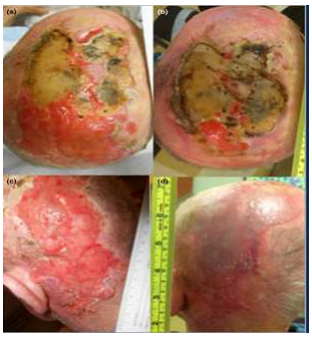
Grade ≥3 TEAEs occurring in >1 patient
- Hypertension (n=6; 7.7%)
- Pneumonia (n=4; 5.1%)
- Hyperglycemia and cellulitis (each n=3; 3.8%)
- Breast cancer, fall, hyponatremia, lymphopenia, muscular weakness, pneumonitis, sepsis, and urinary tract infection (each n=2; 2.6%)

Grade ≥3 TEAEs leading to treatment discontinuation
- Pneumonitis (n=2; 2.6%)
- Encephalitis, hepatitis, increased aspartate aminotransferase, pneumonia, and proctitis (each n=1; 1.3%)

Data cut-off date: Sept 20, 2018 (Group 1); Oct 10, 2018 (Group 2)
CSCC, cutaneous squamous cell carcinoma; TEAE, treatment-emergent adverse event.
1. Guminski et al. J Clin Oncol. 2019:37 (suppl; abstr 9526) [poster presentation]. 2. Migden MR, et al. J Clin Oncol. 2019:37 (suppl; abstr 6015) [poster presentation]. 3. Data on File, Regeneron Pharmaceuticals Inc.

PD 1 antibodies in SCC

Beafore treatment



After treatment

Boradori et al. Br J Dermatol, 2016. 175: 1382-6

Summary

- NMSC - the most common cancer
- Incidence is rising
- Numerous mutations in UV-induced cancer
- Surgery is a standard therapy for non-complicated cases
- Limited role of radiotherapy despite radiosensitivity in MCC

Thank you

NCCN Guidelines. V2.2018. https://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf. Accessed 29 Aug 2018.

Onkološki inštitut
Institute of Oncology
Ljubljana

SKIN TOXICITY OF IMMUNOTHERAPY
CASE PRESENTATION

1st Summer School in medical oncology

Vermiglio Lucija, MD
Dr. Mesti Tanja, MD

PRESENTATION

- B. L., male, 58 years
- History of illness Ø
- PS WHO 1
- July 2017 – **painful mass in the right armpit (12x10x9cm)**
- Biopsy – **Malignant melanoma metastasis**
- Primary tumour Ø
- ↑ S-100, normal LDH
- **BRAF +**
- PET-CT

FIRST LINE TREATMENT

- **BRAF/MEK inhibitors**: vemurafenib 960mg/12h/cont + cobimetinib 60mg/day/3weeks
  - July to Oct 2017
  - Tumor size ↓ 50%
- November 2017 – **Axillary lymph node resection.** 50% ↓ (3x3x3cm), R2 resection, N(9/22)
- December 2017 – **BRAF/MEK inhibitors**
- January – March 2018, **RT** TD 60Gy

SECOND LINE TREATMENT

- May 2018 – **PD** on PET-CT
- Immunotherapy – **Pembrolizumab** 200 mg
- Palliative RT TD 15Gy

- *June 2018 – the **last application of immunotherapy***

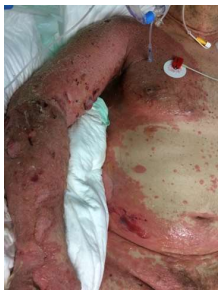
Locoregional status

June 2018:

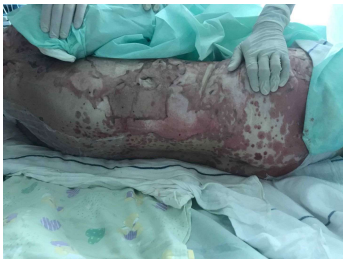
- 4x3cm painfull mass in the right armpit, exulcerated, purulent discharge, right arm red, swollen + osteolitic areas in the right humerus, no fracture
- US arm – no DVT
- Amoxycillin + clavulanic acid
- Antibiogram: Aerobic (Enterococcus faecalis, Staphylococcus lugdunensis, Staphylococcus caprae, Corynebacterium simulans) + Anaerobic bacteria (Prevotella bivia, Peptoniphilus harei, Finegoldia magna, Veilonella atypica)
- Vancomycin + Metronidazol + Ciprofloxacin
- **Severe generalized epidermolysis bullosa** (50 – 60%)
- July 2018 – ICU
- **Septic shock and multiorganic failure**

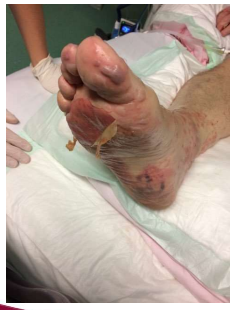
SKIN BIOPSY

- Total necrosis of the epidermis – **toxic epidermal necrolysis**
- Immunofluorescence analysis: IgA mediated Epidermolysis bullosa
- Negative anti BP180 and anti BP230 (pemphigus bullosa)
- Possible anti-P450 pemphigus bullosa or pemphigus bullosa mediated by anti-Plectin Ab

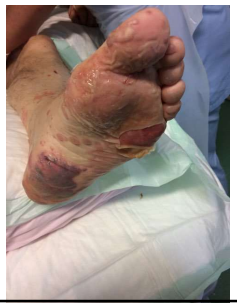


EPIDERMOLYSIS BULOSA



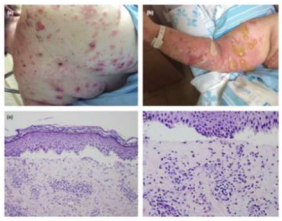


EPIDERMOLYSIS BULOSA



Severe bullous pemphigoid associated with pembrolizumab therapy of metastatic melanoma with complete regression

O. Rote,* G. Bar-Sela,* Z Keidar,* T. Sezin,** C. D. Sadik* and R. Bergman*



Case Reports in Dermatology

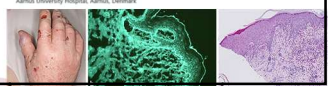
Case Rep Dermatol 2018;10:154–157

Case Series

Bullous Pemphigoid as an Adverse Reaction to Pembrolizumab: Two Case Reports

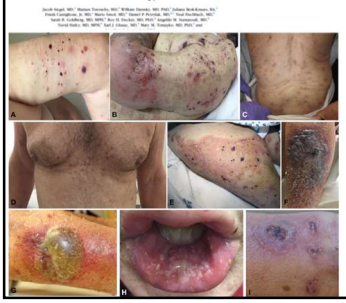
Kenneth Thomsen* Jon Diemaes* Trine Heide Ollegaard* Eva Spaun* Christian Vestergaard*

*Department of Dermatology, Aarhus University Hospital, Aarhus, Denmark; *Department of Oncology, Aarhus University Hospital, Aarhus, Denmark; *Department of Pathology, Aarhus University Hospital, Aarhus, Denmark



Bullous disorders associated with anti–PD-1 and anti–PD-L1 therapy: A retrospective analysis evaluating the clinical and histopathologic features, frequency, and impact on cancer therapy

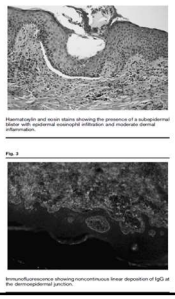
J Am Acad Dermatol Volume 79, Number 6



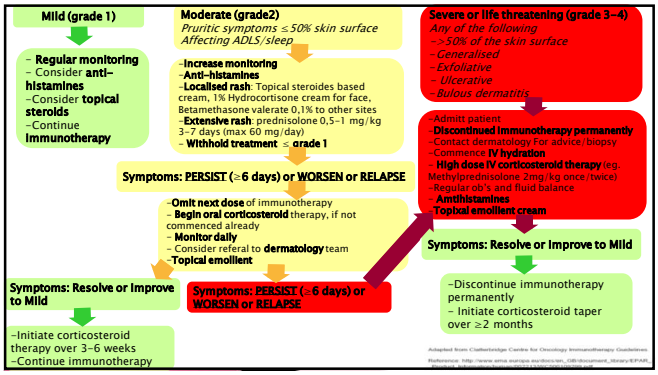
Melanoma Research 2015, 25:265–268

A case of bullous pemphigoid in a patient with metastatic melanoma treated with pembrolizumab

Giuliana Carlos[a,d], Rachael Anforth[a,d], Shaun Chou[b], Arthur Clements[c,d] and Pablo Fernandez-Peñas[a,d]



PREVENTION?




Thank you

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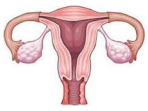
Systemic treatment of ovarian cancer



Erik Škof

1st Summer School in medical oncology – Standards and open questions
Institute of Oncology Ljubljana
6th september 2019

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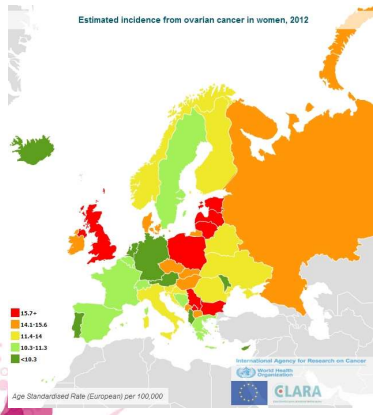
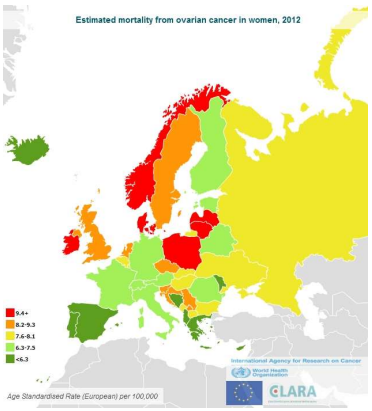
Ovarian cancer burden in Europe



INCIDENCE (per 100.000)
EU : 13,1
SLO: 13,8



MORTALITY (per 100.000)
EU: 7,6
SLO: 9,3

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Ovarian cancer - characteristics

- Despite many improvements in medicine:
  - No effective prevention
  - No effective screening
    - no proven benefit from many studies
  - No early detection
    - no simptoms at early stage
- Result*:
    - >75% of patients have advanced stage at diagnosis (IIIC, IV)
    - 80% of patients have relapse of the disease
    - 5-year overall survival is only about 40%

* Slovenian cancer registry 2016

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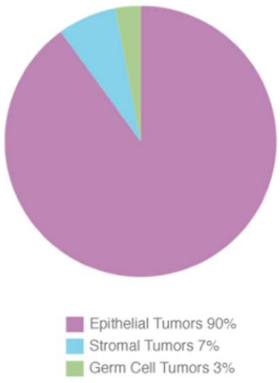
WHO classification of ovarian cancer (2014)

- EPITHELIAL
- STROMAL
- SEX CORD
- GERM CELL TUMORS
- MONODERMAL TERATOMA
- MESOTHELIAL
- SOFT TISSUE
- LIMFATIC AND IN MIELOIC
- SECONDARY (METASTATIC)

MANY COMBINATIONS POSSIBLE
- MORE THAN **80** HISTOLOGY TYPES!



Epithelial ovarian cancer- 5 types

WHO 2014 Diagnostic Criteria per Cancer Type

TYPE	% of total	MOLECULAR CHARACTERISTICS	OTHER NOTES
HGSOC	70%	TP53^{mut}, genomic instability	STIC precursor, no BOT
LGSOC	3.5%	KRAS^{mut}, BRAF^{mut}	Mutations more common in SBOT
CCC	10%	ARID1a^{mut}, PIK3CA^{mut}, PIK3CA^{amp}	15-30% with endometriosis
ENDO ↓gr	10%	ARID1a^{mut}, PIK3CA^{mut}, PTEN LOH, ß catenin^{mut}	EBOT frequency of mutations similar to invasive, 15-30% associated with endometriosis
ENDO ↑gr		TP53^{mut}	Recategorized as HGSOC
Mucinous	3.6%	80%+ KRAS^{mut}	Intestinal type only

BRCA - 20+%

HGSOC: high-grade serous ovarian cancer, LGSOC: low-grade serous ovarian cancer,
CCC: clear cell ovarian cancer, ENDO: endometrial ovarian cancer

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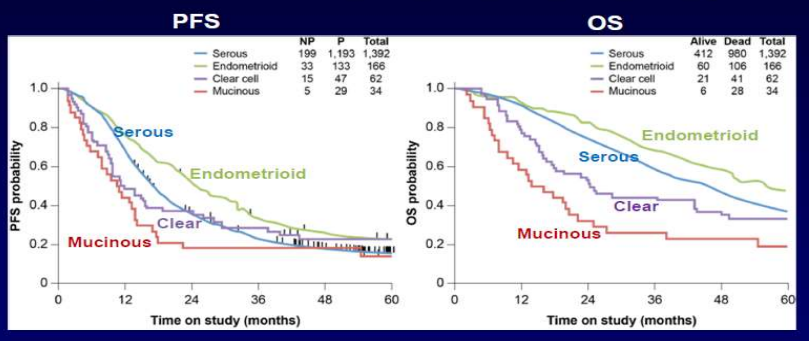
Prognosis depends on histology type

Outcome FIGO Stage III Ovarian Cancer
(GOG Trials #111, 114, 132, 152, 158, 172)



Winter WE 3rd, et al. *J Clin Oncol.* 2007;25(24):3621-3627.

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Systemic treatment of epithelial ovarian cancer

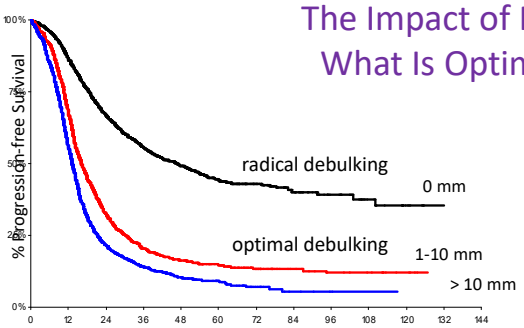
Treatment guidance by histologic type

TYPE	% Early stage presentation	Histology-specific treatment guidance	
HGSOC	20%	Chemotherapy, anti-angiogenic therapy, DNA repair inhibition therapy, radiation	Bevacizumab Olaparib
LGSOC	30+%	*Consensus conference: chemotx or clinical trial	HT
CCC	25%	*	
ENDO	30%	*, **	HT
Mucinous	? all	*Is advanced stage/metastatic ovarian? r/o GI source	

* No validated type-specific treatment
**High grade reclassified and treated as HGSOC

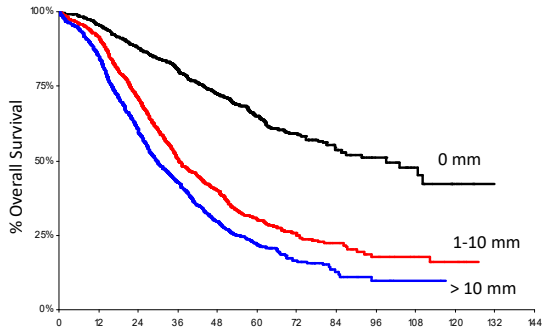
HGSOC: high-grade serous ovarian cancer, LGSOC: low-grade serous ovarian cancer, CCC: clear cell ovarian cancer, ENDO: endometrial ovarian cancer

The Impact of Residual Tumor: What Is Optimal Debulking?



	HR	(95%CI)
1-10 mm vs. 0 mm:	2.52	(2.26;2.81)
>10 mm vs. 1-10 mm:	1.36	(1.24;1.50)

log-rank: p < 0.0001



Generated from 3 prospective Phase III trials (OVAR 3,5, & 7) N = 3126 pts

	HR	(95%CI)
1-10 mm vs. 0 mm:	2.70	(2.37; 3.07)
>10 mm vs. 1-10 mm:	1.34	(1.21; 1.49)

log-rank: p < 0.0001

DuBois, Cancer (2009)115:1234

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Ovarian cancer: primary systemic treatment

- Postoperative (adjuvant)
  - goal is cure (stage I-III)
  - goal is life prolongation (stage IV)
- Preoperative (neoadjuvant)
  - goal is radical debulking at interval surgery - cure?
- Paliative
  - goal is decrease disease symptomes
  - goal is improvement of QoL

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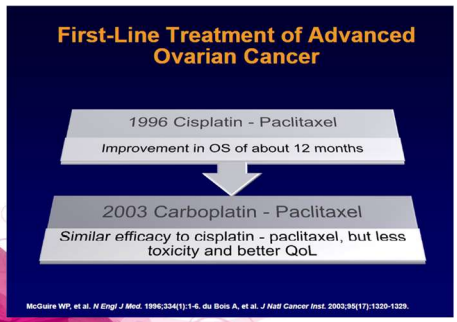
Ovarian cancer: primary systemic treatment

- Chemotherapy
  - platinum + taxane
    - majority of patients (except stage IA, grade I)



OS – overall survival

QoL – quallity of life

Cisplatin+ Ciklofosfamid: OS 24 months.

↓ + 14 mon

Cisplatin+ Paklitaksel: **OS 38 months.**

↓

Karboplatin + Paklitaksel:

- standard
- all histology types

OS similar
less toxic
better QoL

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Ovarian cancer: primary sistemic treatment

Bevacizumab

Recombinant humanised monoclonal anti-VEGF antibody developed from the mice anti-VEGF antibody (MAb A4.6.1)

- 93% of antibody has human origin
- Recognises all human isomorphes of human VEGF molecule
- Blood half-time is 21 days

VEGF = vascular endothelial growth factor
MAb = monoclonal antibody

Presta LG, et al. Cancer Res 1997;57:4593–9

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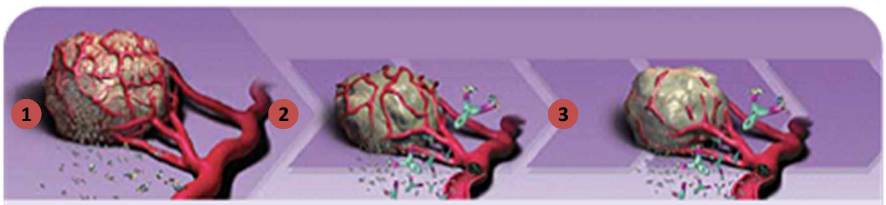
Ovarian cancer: primary systemic treatment

Bevacizumab – mechanism of action

Early effect

Late effect



Inhibition of new blood vessels growth and dissapperance of already formed blood vessels [1,2,3].

Normalisation of remaining tumor vessels offers effective delivery of citotoxic drugs to the tumor cells[1,4,5].

Inhibition of de-nuovo tumor blood vessels leads to tumor shrinkage [2,3,4].

1. Willet et, al. Nat Med 2004; 2. Baluk, et al. Curr Opin Genet Dev 2005; 3. Inai, et al. Am J Pathol 2004; 4. Gerber, et al. Cancer Res 2005; 5. Jain, et al. Science 2005

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Ovarian cancer: primary systemic treatment

The role of bevacizumab

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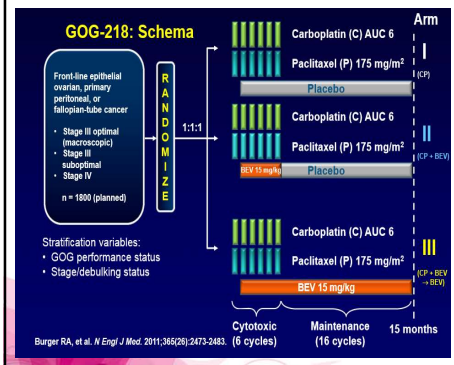
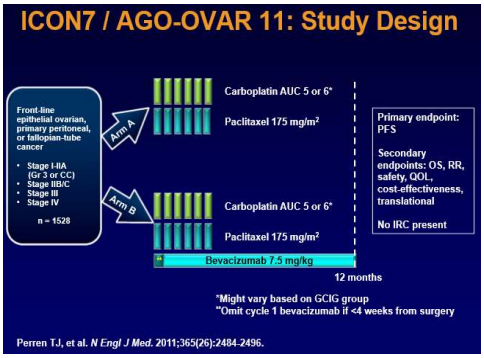
Ovarian cancer: primary sistemic treatment

The role of bevacizumab:





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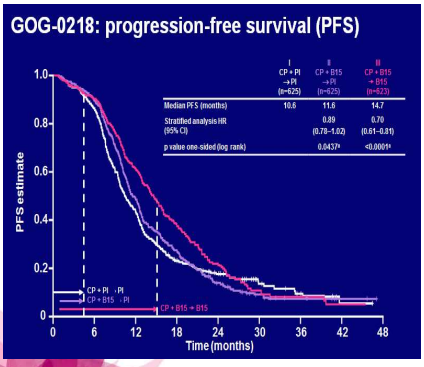
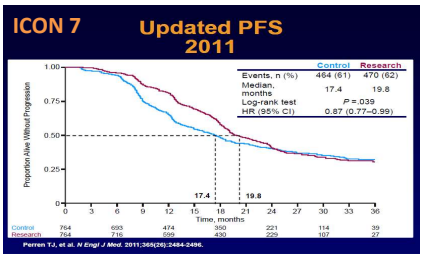
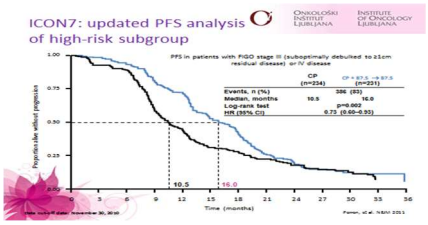
Ovarian cancer: primary systemic treatment

The role of bevacizumab – prolongs PFS



*p value boundary = 0.0116
Data cut-off date: 25 February 2010





PFS – progression-free survival

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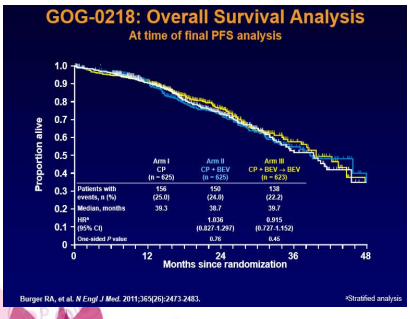
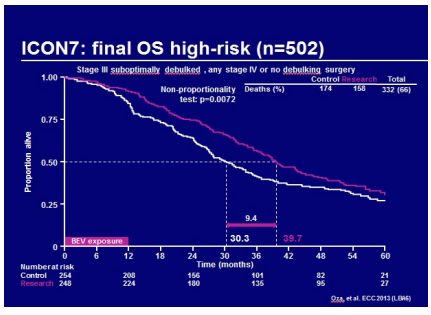
Ovarian cancer: primary systemic treatment

The role of bevacizumab





– overall survival benefit in ICON 7 „high-risk patients“

The role of neoadjuvant chemotherapy

- definition of operable/inoperable disease?

Role of Radical Surgery and Neoadjuvant Chemotherapy in Advanced Ovarian Cancer: Report on the Consensus Paper

Gynecologic Oncology 128 (2013) 6–11
Contents lists available at SciVerse ScienceDirect
Gynecologic Oncology
journal homepage: www.elsevier.com/locate/ygyno

Clinical Commentary

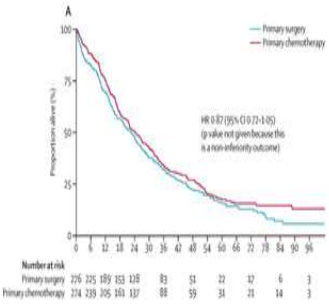
Neoadjuvant chemotherapy in advanced ovarian cancer: On what do we agree and disagree?

Vergote I, du Bois A, et al. *Gynecol Oncol.* 2013;128(1):6-11.

The role of neoadjuvant chemotherapy

- two randomised studies: no difference in OS

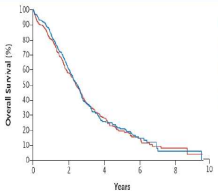
CHORUS
Overall Survival



Kehoe S, et al. Lancet 2015

NACT + IDS vs PDS: ITT Overall Survival

EORTC



Median survival
PDS: 29 months
IDS: 30 months
HR for IDS:0.98
(0.84, 1.13)

	No. of Events	No. of Patients at Risk				
Primary Debulking Surgery (PDS)	253	336	189	62	14	2
Neoadjuvant Chemo-therapy (NACT)	245	334	195	46	13	2

PDS
NACT

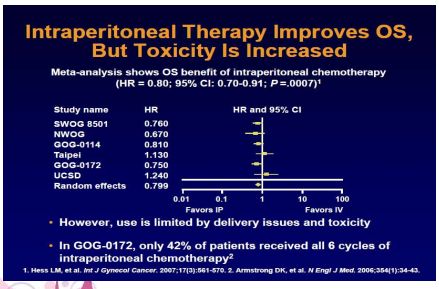
Vergote I, et al. *N Engl J Med.* 2010;363(10):943-953.

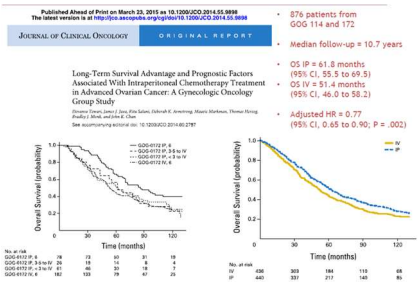
Criticism:

- poor surgery in both studies
- only 20% of pts had radical primary debulking

The role of intraperitoneal chemotherapy-1

Effective but toxic





Criticism:

- old i.v. chemotherapy used,
- inapropriate doses of i.v. chemotherapy,...

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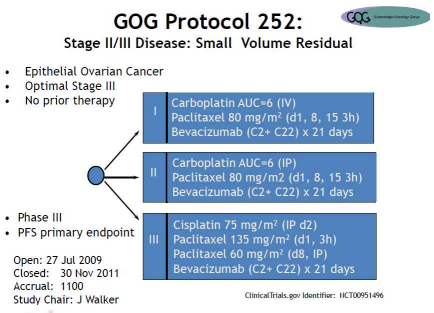
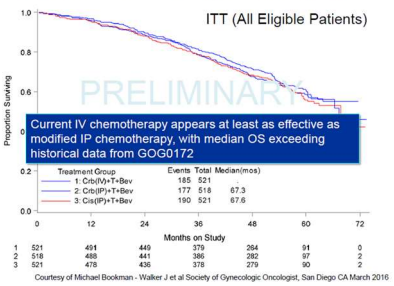
The role of intraperitoneal chemotherapy-2





Conclusions:

Up-to date i.v. chemotherapy with bevacizumab is:

- as effective as i.p. cht (the same OS)
- less toxic
- In EU intraperitonal cht is experimental only treatment

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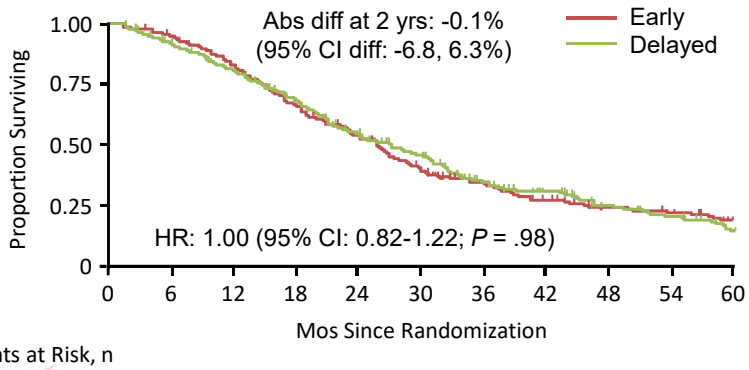
Systemic treatment of relapsed ovarian cancer

When to treat relapsed disease?

EORTC 55955 – CA 125 elevation vs. Clinical/radiologic relapse



Patients at Risk, n

Early	265	247	211	165	131	94	72	51	38	31	22
Delayed	264	236	203	167	129	103	69	53	38	31	19

Rustin G, et al. ASCO 2009.

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Systemic treatment of relapsed ovarian cancer:

Predictive and prognostic factors that influence the treatment selection:

Disease related:

- Platinum-free interval
- Response to prior chemotherapy
- Histology type
- Molecular (BRCA)
- Simptoms

Patient related:

- Performens status
- Age
- Side effects
- Comorbidities
- Patient wishes (hair, etc.)

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Systemic treatment of relapsed ovarian cancer:

Resistance to platinum (PFI<6 months)	Partial sensitivity to platinum (PFI 6-12 months)	Full sensitivity to platinum (PFI>12 months)
Non-platinum cht - monotherapy - ORR: 10-30% - OS: <12 months	Cht – platinum comb. • ORR: 30-60% • PFS : 7 months • OS: 23 months	Surgery Cht – platinum comb. -ORR: 60+% - OS: 30+ months
- PLD - Docetaxel - Etoposide (oral) - Gemcitabine - Topotecan - Paclitaxel (weekly) - bevacizumab	Pakli + Karbo PLD + Karbo Gem + Karbo PLD + trabektidin olaparib bevacizumab	• Pakli + Karbo • PLD + Karbo • Gem + Karbo • Olaparib • bevacizumab

ORR – objective response rate; PFS – progression-free survival, OS – overall survival

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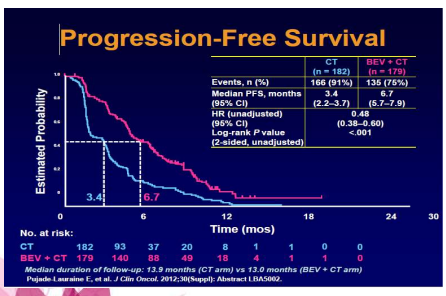
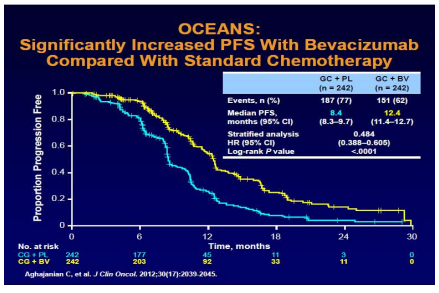
Systemic treatment of relapsed ovarian cancer

Bevacizumab

PFI<6 mes:
AURELIA: prolongs PFS for 3 months



PFI>6mes:
OCEANS: prolongs PFS for 4 months



PFS – progression-free survival
OS – overall survival

No benefit in OS

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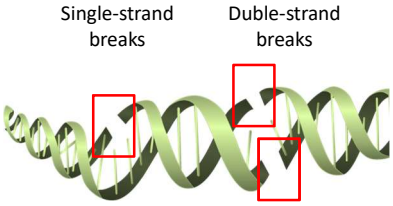
Systemic treatment of relapsed ovarian cancer

Olaparib - PARP inhibitor*

INHIBITS SINGLE-STRAND DNA REPAIR



Olaparib

Base excision Repair **(BER)**

Homologous recombination **(HR)**

BRCA 1/2 mutation

** polyADP ribose polymerase*

- In base excision repair (BER), a damaged base is excised resulting in the formation of a single-strand break, which is enzymatically repaired.
- Two principal mechanisms are used in the repair of double-strand breaks: homologous recombination (HR) and non-homologous end joining (NHEJ)

Jackson SP and Bartek J. Nature 2009;461:1071–1078

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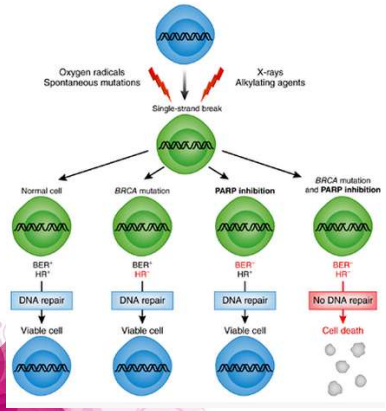
PARP inhibition in preexisting HR deficit:

Olaparib – the princip of synthetic lethality



PARP - polyADP ribose polymerase; HR – homologous recombination

Synthetic lethality

Synthetic lethality is the term used when defects in two pathways lead to cell death, while a defect in either of the individual pathways is not deleterious[2]

PARP inhibition impairs the repair of single-strand breaks[1]

Single-strand breaks lead to replication fork collapse and the occurrence of double-strand DNA breaks during DNA replication[2]

HR mechanism repairs double-strand DNA breaks

1. Jackson SP and Bartek J. Nature 2009;461:1071–1078;
2. De Lorenzo SB et al. Front Oncol 2013;3:228;

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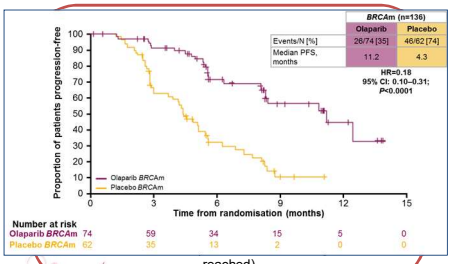
Systemic treatment of relapsed ovarian cancer

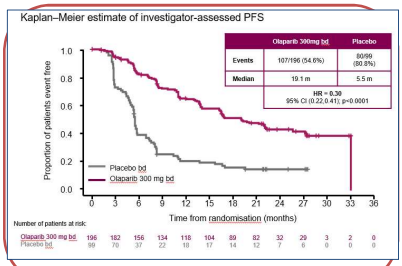
Olaparib maintenance treatment improves PFS in patients with platinum sensitive relapsed ovarian cancer[1-3]

Study 19

solo2 BRCAm Ovarian Cancer



reached)



- PFS = progression-free survival; CR = complete response; PR = partial response; po = per oral; bid = twice a day; HR = hazard ratio; CI = confidence interval
- 1. Ledermann J, et al. N Engl J Med. 2012;366(15):1382–1392; 2. Gourley C, et al. J Clin Oncol 2017;35(suppl); poster related to abstr 5533; 3. Pujade-Lauraine E, et al. Lancet Oncol. 2017 Sep;18(9):1274-1284

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Ovarian cancer: Slovenia

- Since 2014:
  - All patients with HGS* cancer of ovaries, fallopian tubes or PPSC are offered to perform germline BRCA genetic testing **at diagnosis** (or at relapse)
  - The aim of BRCA genetic testing is **treatment with olaparib** (not just prevention of breast and ovarian cancer)
  - Active searching for BRCA+ patients (confidential data)
- Since 2019:
  - All patients with HGS* cancer of ovaries have somatic BRCA testing **at diagnosis**

HGS* - high-grade serous

Zhang S, et al. Gynecol Oncol. 2011;121(2

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SOLO-1 - Phase III trial to investigate maintenance therapy with olaparib in newly diagnosed BRCAm ovarian cancer

SOLO-1 is a global randomised multicentre placebo controlled Phase III study

- Newly diagnosed, FIGO stage III–IV, high-grade serous or endometrioid ovarian, primary peritoneal or fallopian tube cancer
- Germline or somatic *BRCA*m
- ECOG performance status 0–1
- Cytoreductive surgery*
- In clinical complete response or partial response after platinum-based chemotherapy

Olaparib 300 mg bid (N=260)

2:1 randomisation

Stratified by response to platinum-based chemotherapy

Placebo (N=131)

- Study treatment continued until disease progression
- Patients with no evidence of disease at 2 years stopped treatment
- Patients with a partial response at 2 years could continue treatment

2 years' treatment if no evidence of disease

Primary endpoint

- Investigator-assessed PFS (modified RECIST 1.1)

Secondary endpoints

- PFS using BICR
- PFS2
- Overall survival
- Time from randomisation to first subsequent therapy or death
- Time from randomisation to second subsequent therapy or death
- HRQoL (FACT-O TOI score)

*Upfront or interval attempt at optimal cytoreductive surgery for stage III disease and either biopsy and/or upfront or interval cytoreductive surgery for stage IV disease

BICR = blinded independent central review; ECOG = Eastern Cooperative Oncology Group; FACT-O = Functional Assessment of Cancer Therapy – Ovarian Cancer; FIGO = International Federation of Gynecology and Obstetrics; HRQoL = health-related quality of life; PFS = progression-free survival; PFS2 = time to second progression or death; RECIST = Response Evaluation Criteria in Solid Tumours; TOI = Trial Outcome Index; PARP = poly (ADP-ribose) polymerase; *BRCA*m = *BRCA* gene mutation

https://clinicaltrials.gov/ct2/show/NCT01844986 (accessed October 2018)

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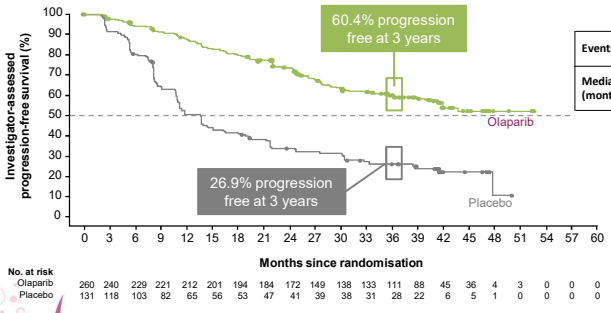
SOLO 1: Olaparib reduced the risk of progression or death by 70% vs. placebo[1]

After a median follow-up of 41 months, the median PFS had not been reached in the olaparib arm (vs. 13.8 months in the placebo arm)[1]



	Olaparib	Placebo
Events, N (%)	102 (39.2)	96 (73.3)
Median PFS (months)	NR	13.8
	HR=0.30 95% CI: 0.23, 0.41 p<0.001	

Primary endpoint: investigator-assessed PFS

DCO: May 2018; Median FU: olaparib, 40.7 months placebo, 41.2 months

Analysis was performed after 198 progression events had occurred (in 50.6% of patients)

PFS = progression-free survival; DCO = data cut-off; HR = hazard ratio; CI = confidence interval

1. Moore K, et al. N Engl. J. Med. (2018) ePub ahead of print; 2. Moore K et al. Oral presentation LBA7_PR, ESMO (2018)

Conclusions

- Platinum based chemotherapy remains backbone in systemic therapy of patients with ovarian cancer
- Bevacizumab and olaparib are used in maintenance setting
- BRCA 1/2 (germline or somatic) testing is recommended in every patient with epithelial ovarian cancer
- Intraperitoneal chemotherapy is „experimental“ treatment in EU

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- Thank you!

APPROACH TO THE PATIENT WITH CANCER AND RENAL IMPAIRMENT/INSUFFICIENCY

Tomaž Milanez
Institute of Oncology Ljubljana
University Medical Center Ljubljana

Epidemiology: renal impairment in patients with cancer

- Elderly patients (65)-higher rate of chronic kidney disease
  - Despite normal serum creatinine levels prevalence of renal in most of those patients is high
  - IRMA study- 65% of patients had renal insufficiency
- NHANES III study -30% (age 53) of patients had renal insufficiency
- IRMA-2 study-
  - renal insufficiency (MDRD - eGFR<60 ml/min/1.73m^2) is independent risk factor for reduced survival
    - Renal insufficiency in the whole was associated with 8.6 reduced median survival compared with normal function (16.4 vs. 25 months: HR = 1.27; p<.0002)

Patients with cancer and renal insufficiency

- Acute kidney injury
- Renal impairment
- Chronic kidney disease (CKD)/Renal insufficiency
  - End stage kidney disease (ESKD)
  - Patients with renal failure on renal replacement therapy
    - Hemodialysis/Peritoneal dialysis
    - Kidney transplantation

How to manage patients with renal impairment

- Acute kidney injury
  - Determining the cause of impairment
  - Managing the life treating features (hyperkaliemia, overhydration/hypervolemia, acidosis, uremic pericarditis)
  - Look for and treat the reversible conditions
    - Lower urinary tract obstruction
    - Intrarenal toxic effects of systemic treatment
  - Avoiding (further) toxic factors
- Chronic renal impairment

How to monitoring renal function in patients with cancer

- Glomerular filtration rate (GFR)
  - Estimation GFR (eGFR)
    - Reference method
    - Different equations (mathematical models)
      - "New model" of eGFR/cisplatin/carboplatin
- Estimating creatinine clearance (CrCl)
- Serum creatinine level

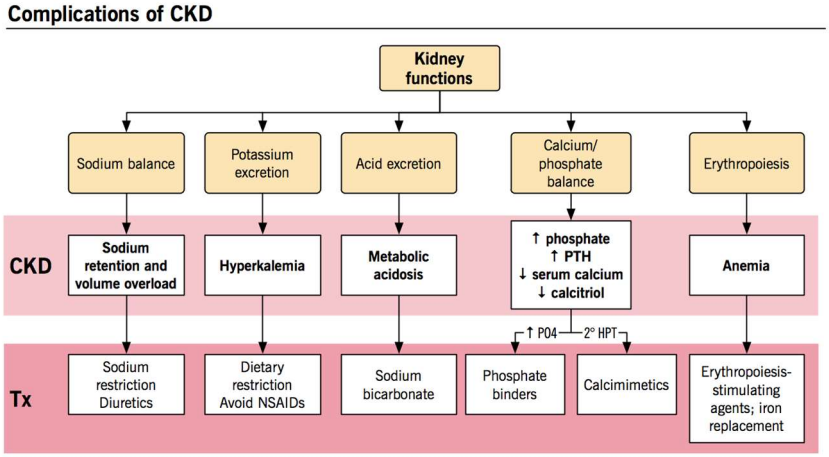
Stages of chronic kidney disease and complications

Table 1. Stages of chronic kidney disease.

Stage	Description	eGFR (mL/min)	Potential complications of reduced GFR (in alphabetical order)
1	Kidney damage with normal or ↑ GFR	≥90	• Anemia, including functional iron deficiency • Blood pressure increases • Calcium absorption decreases • Dyslipidemia /heart failure/volume overload • Hyperkalemia • Hyperparathyroidism • Hyperphosphatemia • Left ventricular hypertrophy • Metabolic acidosis • Malnutrition potential (late)
2	Kidney damage with mild ↓ GFR	60–89	
3	Moderate ↓ GFR	30–59	
4	Severe ↓ GFR	15–29	
5	Kidney failure	<15 or dialysis	

Source: Adapted from Identification, Evaluation and Management of Chronic Kidney Disease (www.health.gov.bc.ca/gpac/pdf/ckd.pdf)

Managing complication of CKD



How to manage the patients with renal impairment and cancer

- Plan of systemic oncological treatment
  - Lack of evidence for systemic treatment for patients with severe renal impairment-insufficiency
    - Patients were exclude from prospective randomized trials
- Managing complications of reduced GFR
- Managing the risk factors of decline of renal function
- Adjusting dose of systemic therapy to renal function/replacement kidney therapy

Patients with cancer and renal insufficiency

- Acute renal failure
  - definition
- Chronic kidney disease (CKD)
  - End stage kidney disease (ESKD)
  - Patients with renal failure on renal replacement therapy
    - Hemodialysis
    - Peritoneal dialysis
    - Kidney transplantation

Profile of cancer patients with renal insufficiency/CKD

- Definition
  - Guidelines of CKD (KDOQI)
- Risk factors (CKD)
  - Comorbidities
- Kidney failure
  - Chronic dialysis treatment (hemodialysis/peritoneal dialysis)
  - Kidney transplant treatment
- Agents known to adversely affect renal function
- “Polypharmacy”

Conclusions

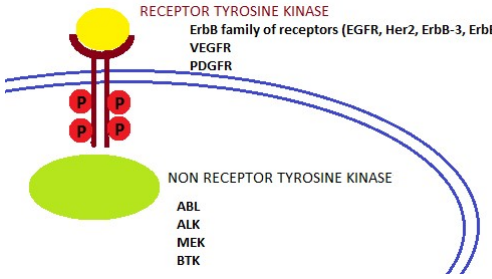
- Follow the goal of systemic oncological treatment-clinical end points/ extend meaning

- Preserve kidney function/capacity of organs/maintain organ function
- Lack of guidelines for systemic treatment in patients with severe renal impairment (recommendation)
- Adjust systemic treatment to renal function
  - Use the most appropriate equation for estimating GFR (systemic treatment – derivatives of platinum)
  - Estimate and monitor renal function (patients with renal failure/insufficiency)/modalities
  - Pharmacokinetics of systemic drugs (guidelines/recommendation)
  - Adjust systemic treatment to replacement therapy i.e. dialysis (recommendation)
- Managing comorbidities and complication of CKD
- Avoiding/replace potential renal toxic drugs/agents
- Looking for reversible factors during the treatment
- Balancing/weighing between potential effectiveness and harm in patients with severe renal impairment (case reports, retrospective analysis)

Toxicity of tyrosine kinase inhibitors and the management

Urška Bokal, MD,
Institute of Oncology, Ljubljana
1st Summer School of Medical Oncology, 6. 9. 2019

Tyrosine kinase inhibitors



- Other protein kinases:
  - B Raf (serine threonine kinase)

Tyrosine kinases:
- active proteins/autoactivates by phosphorylation

- important for signal transductaion and cell cycle regulation

Tyrosine kinase inhibitors:
- Small molecules, oral application
- act mostly by blocking ATP binding site, therefore inhibit phosphorylation
- bind reversibly or irreversibly

ATC classification system

L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS
L01 ANTINEOPLASTIC AGENTS
L01X OTHER ANTINEOPLASTIC AGENTS
L01XE Protein kinase inhibitors

ATC code	Name
L01XE01	imatinib
L01XE02	gefitinib
L01XE03	erlotinib
L01XE04	sunitinib
L01XE05	sorafenib
L01XE06	dasatinib
L01XE07	lapatinib
L01XE08	nilotinib

WHO Collaborating Centre for Drug Statistics Methodology

https://www.whocc.no/atc_ddd_index/?code=L01XE&showdescription=no

On and off target toxicity

- On target:
  - due to inhibition of the desired target (mechanism based)
  - class effect: shared with all agent that inhibit specific target
  - VEGFR TKI: hypertension
  - EGFR TKI: rash
- Off target:
  - due to inhibiton of other unintended targets
  - sunitib: hematologic toxicity (FLT3 inhibition)

CA Cancer J Clin. 2013;63:249-79

The good news: toxicity may correlate with response/better survival

- rash due to EGFR TKI in lung cancer
- hypertension and hypothyroidism due to VEGFR inhibitors in renal cell carcinoma

PLoS One. 2013;8(1):e55128. doi: 10.1371/journal.pone.0055128. Epub 2013 Jan 30.

Skin rash could predict the response to EGFR tyrosine kinase inhibitor and the prognosis for patients with non-small cell lung cancer: a systematic review and meta-analysis.

Liu HB[1], Wu Y, Lv TF, Yao YW, Xiao YY, Yuan DM, Song Y.

J Natl Cancer Inst. 2011 May 4;103(9):763-73. doi: 10.1093/jnci/djr128. Epub 2011 Apr 28.

Hypertension as a biomarker of efficacy in patients with metastatic renal cell carcinoma treated with sunitinib.

Cancer. 2011 Feb 1;117(3):534-44. doi: 10.1002/cncr.25422. Epub 2010 Sep 15.

Hypothyroidism in patients with renal cell carcinoma: blessing or curse?

Schmidinger M[1], Vogl UM, Bojic M, Lamm W, Heinzl H, Haitel A, Clodi M, Kramer G, Zielinski CC.

Liu S et al. Cancer Treat Rev. 2014; 40: 883-91

Anti Her tyrosine kinase inhibitors

Compound	Target inhibition	Specific toxicity
erlotinib gefitinib	1st generation EGFR TKI (mutant EGFR, reversible)	skin related toxicity (rash, acne, pruritus, dry skin) diarrhea interstitial pneumonitis
afatinib dacomitinib	2nd generation EGFR TKI (EGFR, Her2 and Her4, irreversible)	
osimertinib	3rd generation EGFR TKI (mutant EGFR including mutation T790M, irreversible)	
lapatinib	EGFR and Her2, reversible	diarrhea nausea, vomiting rash cardiomyopathy
neratinib	EGFR, Her2 and Her4, irreversible	

anti ALK tyrosine kinase inhibitors

CPK – creatine phosphokinase
AP – alkaine phosphatase

ALL: interstital lung disease!!

Compound	Target inhibition	The most common toxicity (incidence of all grades)	Other toxicity
crizotinib (+ ROS1, cMET)	1st generation ALK TKI	nausea, vomiting, diarrhea, constipation, edema, fatigue, ↓ appetite, neuropathy, dizziness hepatotoxicity, vision disorder, (≥ 25%)	neutropenia, QT prolongation, bradycardia, cardiac failure, GIT perforation, renal impairment
ceritinib (+ ROS1)	2nd generation ALK TKI	nausea, vomiting, diarrhea, constipation, fatigue, ↓ appetite, ↓ weight, abdominal pain, hepatotoxicity, ↑ creatinine, rash, anemia, esophageal disorder (≥ 10%)	QT prolongation, bradycardia, hyperglycemia, ↑ amylase and lipase
alectinib (+ RET)		constipation, edema, myalgia (≥ 20%)	hepatotoxicity, ↑ CPK, bradycardia, photosensitivity
brigatinib (+ ROS1)		↑ glucose, insulin, CPK, lipase, amylase, AP, aPTT, ↓ lymphocytes, phosphate, leucocytes, anemia, nausea, diarrhea, fatigue, cough, headache, rash, vomiting, dyspnea, hypertension, myalgia, peripheral neuropathy (≥ 25%)	bradycardia visual disturbance
lorlatinib (+ ROS1)	3rd generation ALK TKI	hyperlipidemia, peripheral neuropathy, cognitive effects, edema, fatigue, weight increase, diarrhea, arthralgia (≥ 20%)	↑ amylase, lipase, AV block, LVEF decrease

anti VEGFR tyrosine kinase inhibitors

Compound	Specific toxicity
sunitinb pazopanib axitinib tivozanib cabozanitib sorafenib regorafenib	thyroid dysfunction, dysphonia, palmar-plantar erythrodysaesthesia syndrome thromboembolism, hypertension, cardiac failure, QT prolongation hemorrhages, GIT perforation/fistulas, impaired wound healing liver toxicity, proteinuria, fatigue, taste disorder

Take home message

- Toxicity varies between patients.
- Beware of drug interactions!
- During its management patients may be referred to doctors of other specialities.
- Low grade toxicity importantly influence the quality of life of patients.

IMMUNE-RELATED ADVERSE EVENTS OF IMMUNE CHECKPOINT INHIBITORS

Nežka Hribernik, MD
Martina Reberšek, MD, PhD
Institute of Oncology Ljubljana

1st Summer School in Medical Oncology
September 2019

Characteristics of irAE

- They are reversible if treated promptly
- If left untreated they progress to more severe state
- If treated early, severity and duration decreases
- Any organ can be affected
- Average 6 – 12 weeks after initiation of therapy
- Can occur
  - Within days of the first dose
  - After several months of therapy
  - After discontinuation of therapy

Pre-treatment evaluation and diagnostic tests to consider

- **WHO PS**
- **History**
  - **Detailed questioning for autoimmune, infectious disease, endocrine and organ-specific disease history (NOT contraindication, but should be well controlled!)**
  - **History of base line bowel habit (frequency of bowel movements, usual stool consistency)**
- **Blood tests:**
  - **CBC, CMP, TSH/T3/T4**, HbA1c, total CK
  - **Infectious disease screen**: HBsAg/sAb/cAb,HCAb, CMV Ab, HIV Ab/Ag p24
- Dermatologic examination
- Pulmonary test (SaO_2), cardiac tests (ECG, Trop I/T)
- Additional screening tests recommended in patients with pre-existing organ disease/at risk of organ-specific toxicity (8 am ACTH, cortisol, NT pro-BNP, 6MWT ...)

General approach to management of irAEs

Grade	Management	ICI	Notes
1	Supportive measures Close monitoring	Continue (exept some: pneumonitis/ neurological/ cardias irAEs)	Outpatient
2	Corticosteroids Immediate vs delayed	Withhold ICI (continued once AEs ≤ G1)	Outpatient with close team contact or inpatient
3	Immediate corticosteroids and additional IMA if required	Withhold or discontinue ICI	Inpatient (except some: skin/ hepatitis)
4	Immediate corticosteroids With early use of additional IMA	Discontinue ICI	Inpatient Consider transfer to experienced centre!

Puzanov I, et al. J Immunother Canc 2017; L Spain ESMO 2018

- Development of irAE is not required for ICIs benefit; some irAE (e.g., vitiligo) may be more clearly associated with **ICIs efficacy.**
- **The clinical outcome** of patients on ICIs is not affected by the use of immunosuppressive agents or the management of irAE.
- **Reintroducing ICIs** should be made on an individual basis, taking into account the clinical setting and specific clinical need of each patient (severity of initial irAE, age).
- **Age** alone should not be used to exclude patients from treatment, benefit appears to be similar regardless of age.

TAKE-HOME MESSAGES!

- MULTIDISCIPLINARY APPROACH
  - Baseline assessment
  - Ongoing assessment
  - PATIENT & PHYSICIAN EDUCATION
  - Management protocols
  - Collaboration with emergency departments, GPs, specialists, visiting nurses!!
- AWARENESS IS NEEDED AMONG CLINICIANS ACROSS DISCIPLINES GIVEN THE INCREASE IN USE OF THESE AGENTS.

APENDIX:

Dr. Dobrila: Systemic treatment of metastatic gastric cancer
(Tuesday 03.09.)

Dr. Pleština: Systemic treatment of metastatic colorectal cancer
(Tuesday 03.09.)

Dr. Škrbinc: Systemic treatment of germinal tumors

(Wednesday 04.09.)

Systemic treatment in advanced gastric cancer

Prof. Renata Dobrila-Dintinjana, MD.PhD.
Clinical Hospital Center, Rijeka
School of Medicine, Rijeka
Croatia

Advanced Gastric Cancer

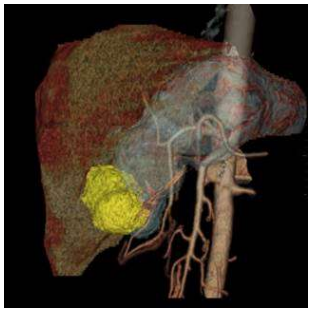
Locally advanced

OS: 11 months

Resectability

(Same survival of initially resectable patients)

A 3-drug regimen (tumor response)



Metastatic

OS: 3 months

Palliation

QoL; Survival

A 2-drug regimen

(no toxic regimen)

Cascinu S, et al. Br J Cancer 2004.

Locally advanced disease:
1.The most active regimen?
2.The role of surgery?

Triplet vs doublet:

Better Response
40/50% vs 20/30%

Which regimen?
FLOT

pCR
- ***FLOT 16%***
- ***ECX 11%***
- ***CDDP/5FU 3%***

Full Paper
High curative resection rate with weekly cisplatin, 5-fluorouracil, epidoxorubicin, 6S-leucovorin, glutathione, and filgastrim in patients with locally advanced, unresectable gastric cancer: a report from the Italian Group for the Study of Digestive Tract Cancer (GISCAD)

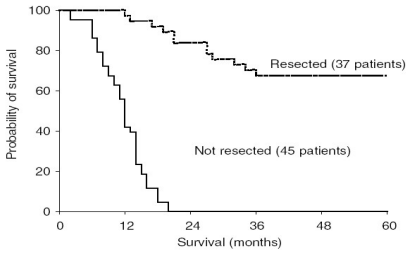


Figure 2 (**A**) Kaplan–Meier overall survival (OS) curve for the whole group of 82 patients. (**B**) Kaplan–Meier survival curves for patients who underwent curative resection of primary gastric tumour after chemotherapy (resected, - - - - -), and for not resected patients (not resected, ———).

Cascinu S, et al. *Br J Cancer* 2004.

Molecular Characterization of Gastric Carcinoma: Therapeutic Implications for Biomarkers and Targets

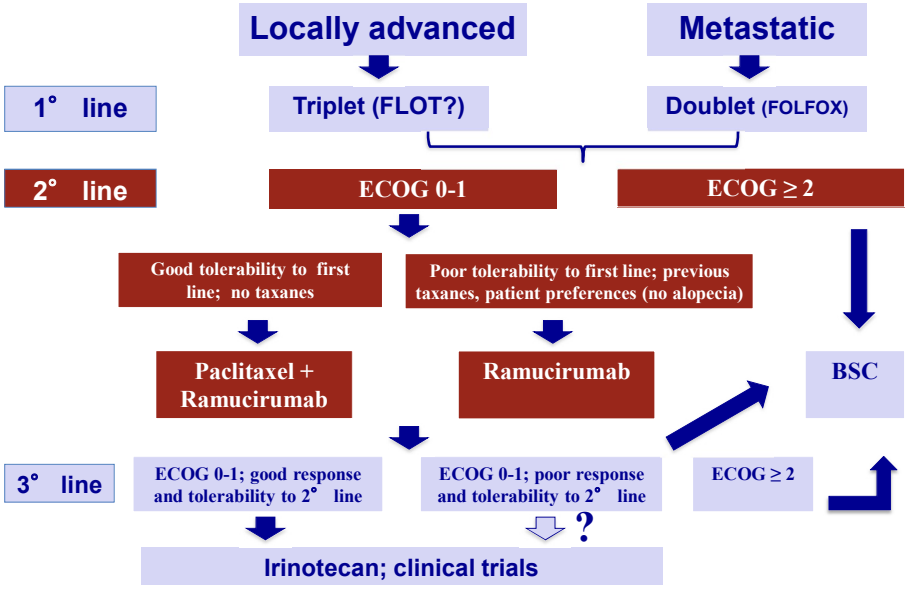
- *NO biomarker is available for predicting treatment response in the individual patient except human epidermal growth factor receptor 2 (HER2) amplification and programmed death-ligand 1 (PD-L1) expression for effectiveness of trastuzumab and pembrolizumab.....*
- *Molecular classification of GC by The Cancer Genome Atlas Research Network and the Asian Cancer Research Group is expected to identify therapeutic targets and predictive biomarkers.*

Subtypes	Targets	Targeted Agents
EBV	PIK3CA	Idelalisib, Taselisib
	PD-L1/L2	Pembrolizumab, Nivolumab, Durvalumab, Avelumab, Atezolizumab
MSI	MLH1 silencing	Pembrolizumab, Nivolumab, Durvalumab, Avelumab, Atezolizumab
	PIK3CA,	Idelalisib, Taselisib
	EGFR	Erlotinib, Gefitinib
	ERBB2	Trastuzumab
	ERBB3	Pertuzumab
	PD-L1	Pembrolizumab, Nivolumab, Durvalumab, Avelumab, Atezolizumab
CIN	EGFR	Erlotinib, Gefitinib
	VEGFA	Bevacizumab, Ramucirumab
	CCNE1, CCND1, CDK6	Palbociclib, Ribociclib, Abemaciclib
GS	RHOA	-
	CLDN18	-

Lionel Kankeu Fonkoua 1 and Nelson S. Yee 2,*Molecular Characterization of Gastric Carcinoma: Therapeutic Implications for Biomarkers and Targets. Biomedicines **2018**, 6, 32; doi:10.3390/biomedicines6010032www.mdpi.com/journal/biomedicines

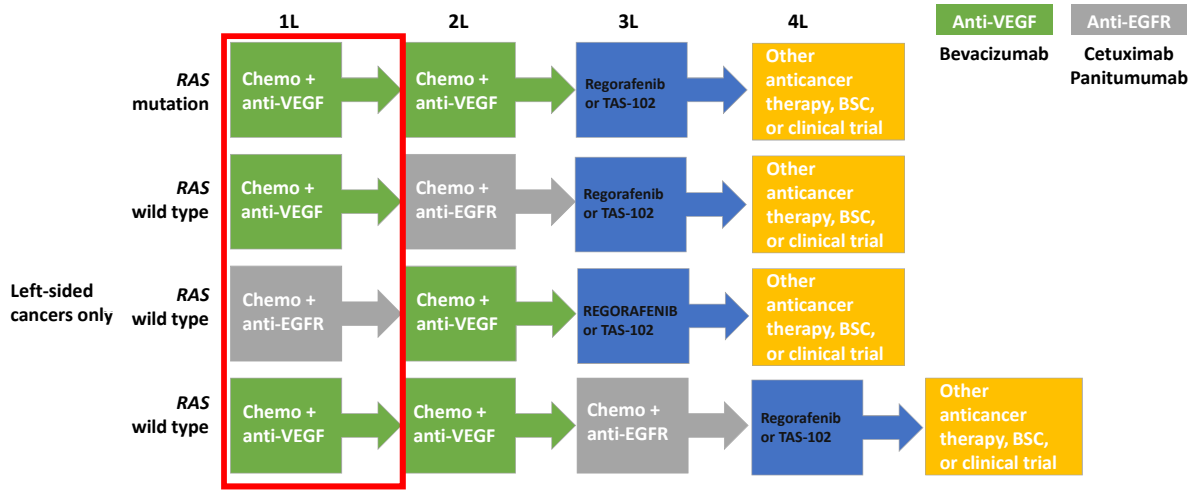
Proposed treatment algoritm

(Salati et al. *ESMO Open* 2017;2:e000206. doi:10.1136/esmoopen-2017-000206)

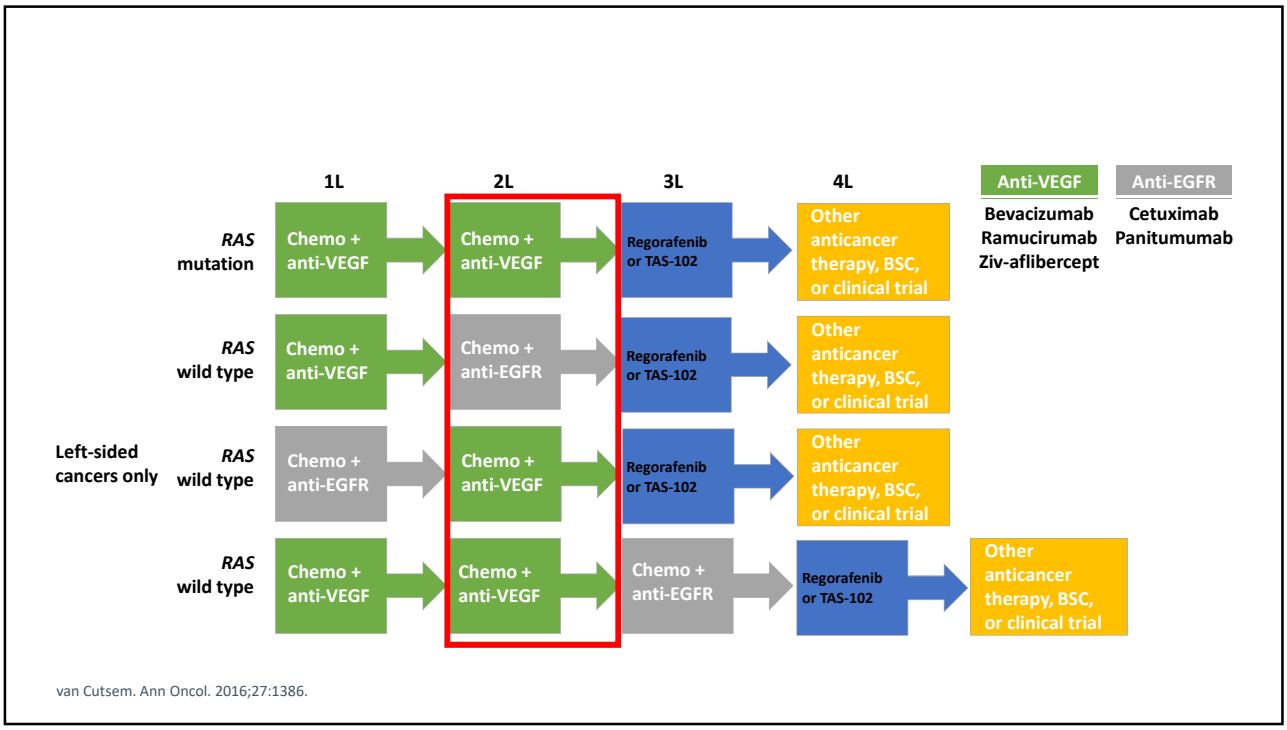


Systemic treatment of metastatic colorectal cancer

prof.dr.Stjepko Pleština
Department of Oncology
UHC Zagreb, Croatia



van Cutsem. Ann Oncol. 2016;27:1386.



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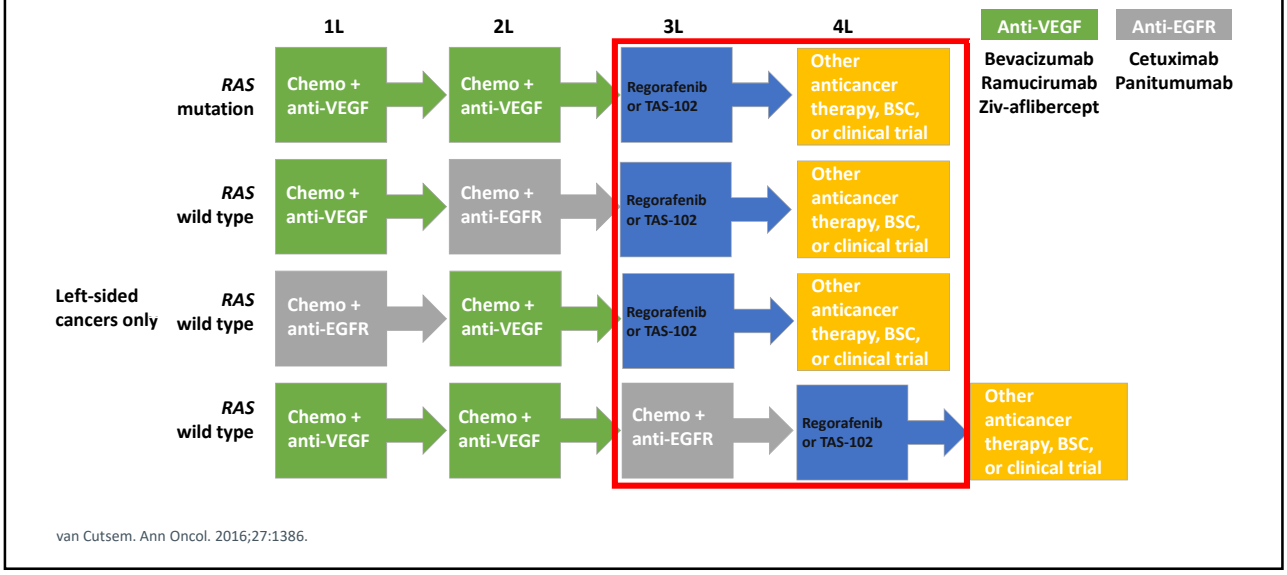


van Cutsem. Ann Oncol. 2016;27:1386.

- A wealth of evidence indicates that primary tumour location is prognostic
  - Patients with left-sided tumours have longer survival outcomes than patients with right-sided tumours
  - The prognostic value appears independent of chemotherapy backbone
- Genetic differences between right- and left-sided tumours may account for some of the prognostic effect
  - Right-sided primary tumours occur more frequently with increasing age and are more likely to have concomitant genetic features associated with poor outcomes: BRAF MT, MSI-H, and increased methylation
- Both clinical trial and real-world data suggest that bevacizumab provides clinical benefit regardless of primary tumour location
- The totality of data suggests that cetuximab and panitumumab have efficacy in left-sided CRC, but EGFR inhibitors are not equaly beneficial to patients with right-sided primary tumours
  - The NCCN guidelines draw the same conclusion that bevacizumab works regardless of tumour location whereas anti-EGFRs are only effective in left-sided tumours: “only patients whose primary tumours originated on the left side of the colon (splenic flexure to rectum) should be offered cetuximab or panitumumab in the first-line treatment of metastatic disease”

REKONIC 2019

Overview of CMS Predictive Data in mCRC

CALGB80405	1st line	*RAS* wild-type	RCT (n=392)	FOLFOX-cetuximab vs. FOLFOX bevacizumab	CMS1 > OS with FOLFOX-bevacizumab, CMS2 > OS with FOLFOX-cetuximab	Almac Xcell FFPE
FIRE-3	1st line	*RAS* wild-type	RCT (n=385)	FOLFIRI-cetuximab vs. FOLFIRI bevacizumab	CMS4 > OS with FOLFIRI-cetuximab	Custom Nanostring FFPE
CAIRO2	1st line	all-comers	RCT (n=311)	CAPOX-bevacizumab vs. CAPOX-bevacizumab-cetuximab	CMS2/CMS3 > OS with cetuximab (*RAS*/*BRAF* wt)	IHC FFPE
MAX	1st line	all-comers	RCT (n=237)	Capecitabine +/- mitomycin +/- bevacizumab	CMS2/CMS3 > PFS with bevacizumab	Almac Xcell FFPE
Japan	1st line	all-comers	Retrospective (n=193)	Oxaliplatin vs. Irinotecan	CMS4 > PFS and OS with Irinotecan	Agilent FF
CORRECT	3rd line	all-comers	RCT (n=)	Regorafenib vs placebo	CMS4 > OS with Regorafenib	Affimetrix Array FFPE

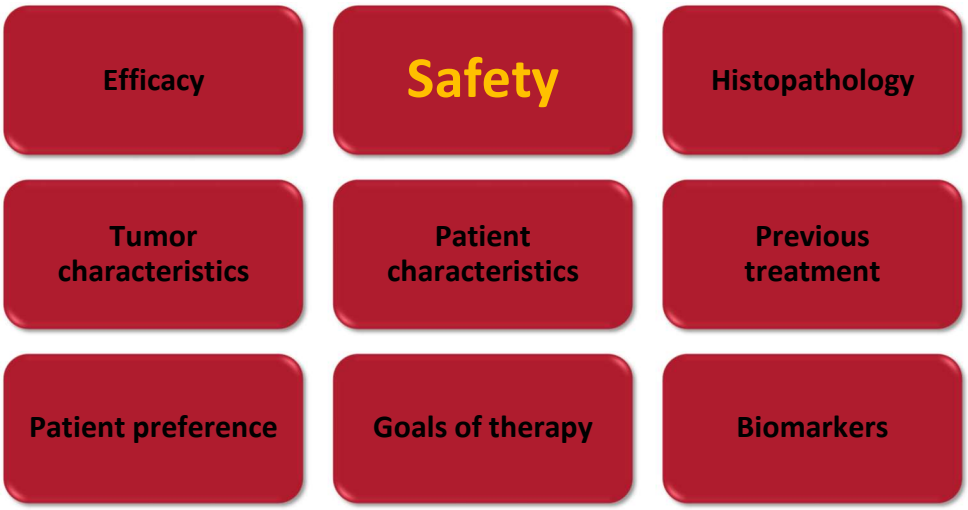
FFPE, Formalin-Fixed Paraffin-Embedded; IHC, immunohistochemistry; OS, overall survival; PFS, progression-free survival; RCT, randomized clinical trial.

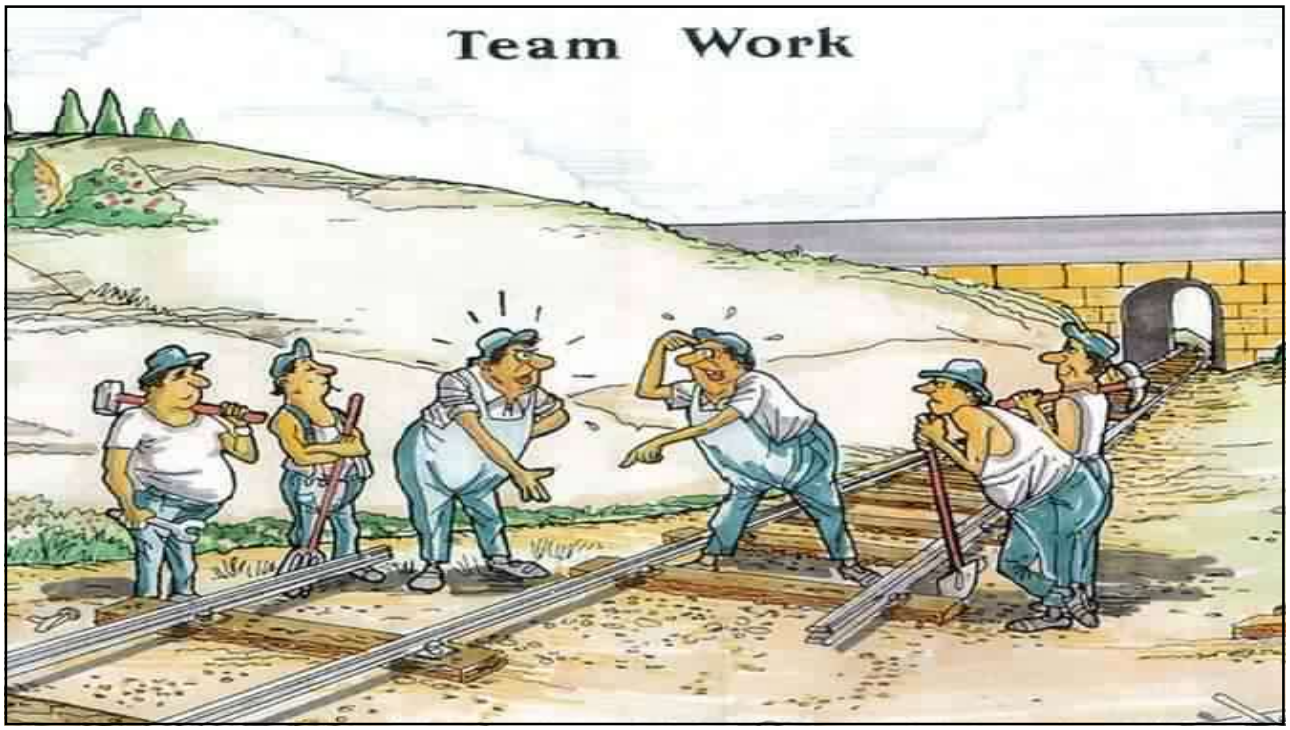
Stintzing S, et al. *J Clin Oncol.* 2017;35(suppl; abstr 3510); Lenz HJ, et al. *J Clin Oncol.* 2017;35(suppl; abstr 3511); Okita A, et al. *Oncotarget*. 2018;9:18698-18711; Teufel M, et al. *J Clin Oncol.* 2015;33(suppl; abstr 3558).

Current Treatment Paradigms in Metastatic Colorectal Cancer

- Better, but still pure prognosis
- Some patients with “limited” stage IV disease can be cured by an interdisciplinary approach
- Addition of biologics to chemotherapy has improved outcomes, but to a more limited extent than hoped
- Identification of molecular predictive factors is improving potential for individualized therapy
- Attempts are under way to expand the role of immunotherapy beyond treating patients with microsatellite instability-high CRC

mCRC – Multidisciplinary Therapeutic Decision…….





ESMO 2017 GUIDELINES

Category	Fit patients						Unfit	
							May be unfit	Unfit
Treatment goal	**Cytoreduction (tumor shrinkage)**			**Disease control (control of progression)**			**Palliation**	
Molecular profile	***RAS* WT**	***RAS* MT**	***BRAF* MT**	***RAS* WT**	***RAS* MT**	***BRAF* MT**	**Any**	**Any**
First line								
Preferred choice(s)	ChT doublet + EGFR antibody	ChT doublet + bevacizumab	FOLFOXIRI + bevacizumab	ChT doublet + bevacizumab or ChT doublet + EGFR antibody	ChT doublet + bevacizumab	FOLFOXIRI +/– bevacizumab	FP + bevacizumab	BSC
Second choice(s)	FOLFOXIRI +/– bevacizumab	FOLFOXIRI +/– bevacizumab	ChT doublet + bevacizumab	FP + bevacizumab		ChT doublet + bevacizumab	Reduced-dose ChT doublet	–
Third choice(s)	ChT doublet + bevacizumab	FOLFOXIRI	FOLFOXIRI				If *RAS* WT may consider EGFR antibody therapy	–
Maintenance								
Preferred choice	FP + bevacizumab	FP + bevacizumab	FP + bevacizumab	FP + bevacizumab	FP + bevacizumab	FP + bevacizumab	FP + bevacizumab	–
Second choice	Pause	Pause	Pause	Pause	Pause	Pause	FP	–
Second line								
Preferred choice(s)	ChT doublet + bevacizumab	ChT doublet + bevacizumab	ChT doublet + bevacizumab	ChT doublet + bevacizumab or ChT doublet + EGFR antibody	ChT doublet + bevacizumab	ChT doublet + bevacizumab		–
Second choice(s)	ChT doublet + EGFR antibody or FOLFIRI + aflibercept/ramucirumab	FOLFIRI + aflibercept/ ramucirumab	FOLFIRI + aflibercept/ ramucirumab	FOLFIRI + aflibercept/ramucirumab	FOLFIRI + aflibercept/ ramucirumab	FOLFIRI + aflibercept/ramucirumab		–
Third line								
Preferred choice(s)	ChT doublet + EGFR antibody or irinotecan + cetuximab	Regorafenib or trifluridine/tipiracil	Regorafenib or trifluridine/tipiracil	ChT doublet + EGFR antibody or irinotecan + cetuximab	Regorafenib or trifluridine/tipiracil	Regorafenib or trifluridine/tipiracil		–
Second choice(s)	EGFR antibody monotherapy			EGFR antibody monotherapy				–
Third choice(s)	Regorafenib or trifluridine/tipiracil			Regorafenib or trifluridine/tipiracil				–

ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY
LJUBLJANA

Systemic treatment of germ-cell tumors

Dr. Breda Škrbinc, dr.med.

OI Ljubljana, 4.9.2019

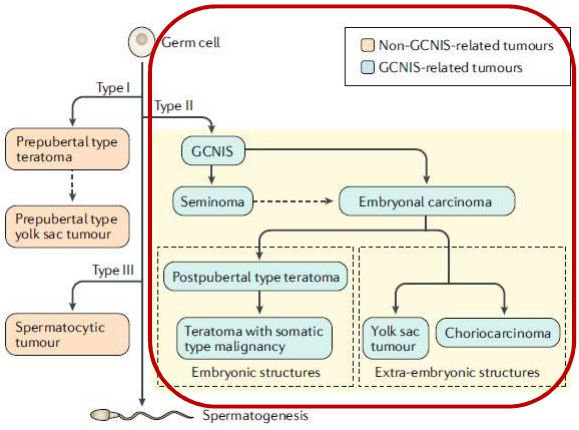


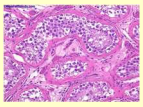
Fig. 1 | **Schematic representation of the types of testicular germ cell tumours**

https://doi.org/10.1038/s41572-018-0029-0
NATURE REVIEWS | DISEASE PRIMERS (2018)

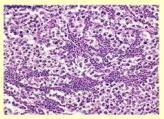
GCT histopathology

Testicular cancers are one of the most diverse areas of human pathology

GCNIS

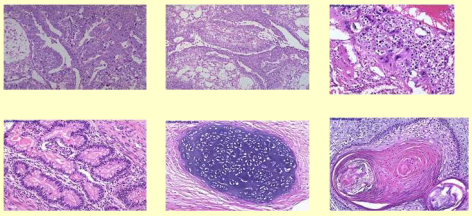


Seminoma (50 %)



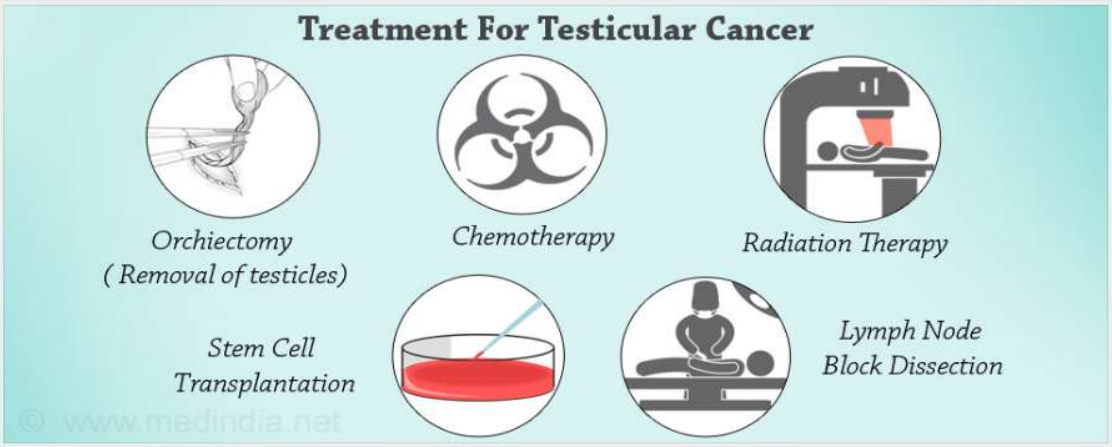
Nonseminoma (40 %)

- **Embrional carcinoma**
- **Yolk sac tumor**
- **Choriocarcinoma**
- **Teratoma postpubertal type**

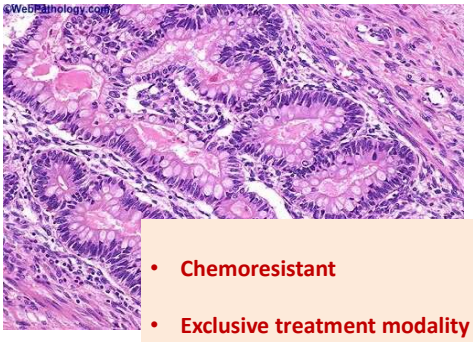


Mixed germ cell tumors (10 %)

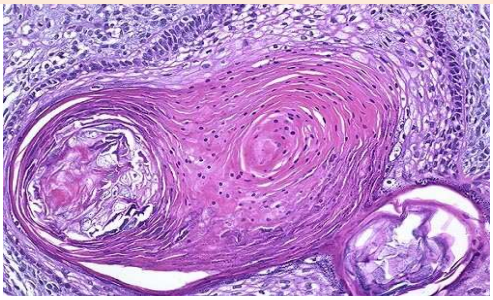
Multidisciplinary treatment

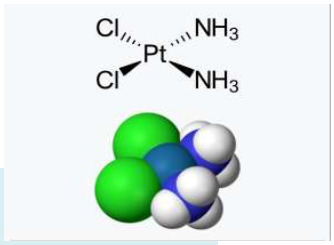


Teratoma postpubertal type

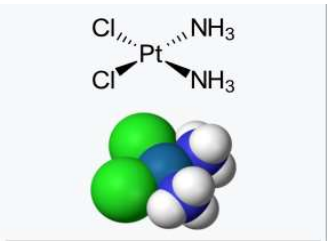


- **Chemoresistant**
- **Exclusive treatment modality – radical surgery**





- **Cisplatine based chemotherapy**
- **Success story in metastatic GCT treatment**
- **70% of mGCT patients cured with first line ChT**
- **30% mGCT relapsing**
  - **up to 70% long term susviviors – one salvage ChT line**
  - **up to 25% long term survivors – 2 or more ChT lines**
- **10–15% of primarily advanced and 3–5% of all GCC patients fail established platinum-based standard treatments and potentially die of the disease**



- **Adjuvant chemotherapy**
- **Chemotherapy for the metastatic disease**
- **Salvage treatment**

Radiotherapy versus single-dose carboplatin in adjuvant treatment of stage I seminoma: a randomised trial

*R T D Oliver, M D Mason, G M Mead, H von der Maase, G J S Rustin, J K Joffe, R de Wit, N Aass, J D Graham, R Coleman, S J Kirk, S P Stenning, for the MRC TE19 collaborators and the EORTC 30982 collaborators**

1477 patients from 70 hospitals in 14 countries randomly assigned to receive:

- **Radiotherapy** (para-aortic strip or dog-leg field)

or

- **one injection of carboplatin**
  dose based on the formula: **7 X [glomerular filtration rate X 25] mg**

The primary outcome measure - **the relapse-free rate**,
with the trial powered to exclude absolute differences in 2-year rates of more than 3%.

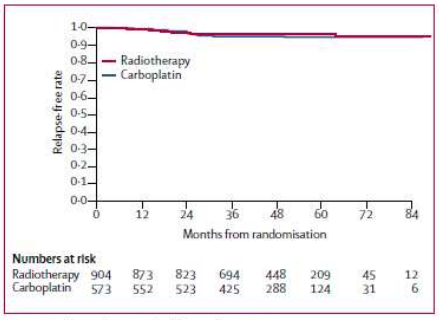
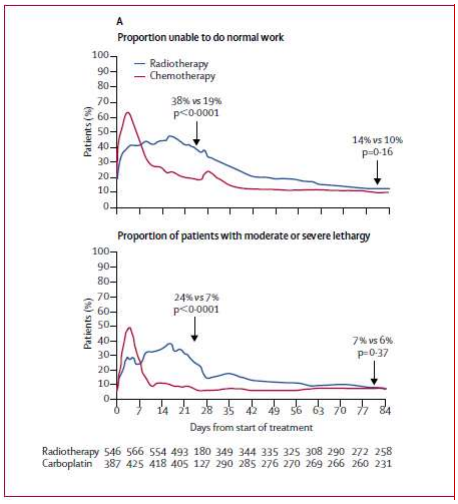


Figure 3: Relapse-free rate by allocated treatment



Patients' diary card data
Comparison between radiotherapy and carboplatin treatment

At 2 years' follow-up, the absolute differences in relapse-free rates (radiotherapy–chemotherapy) were :

- **–1·0% (90% CI –2·5 to 0·5) by direct comparison of proportions**
- **0·9% (–0·5 to 3·0) by a hazard-ratio-based approach.**
- **Patients given carboplatin were less lethargic and less likely to take time off work than those given radiotherapy.**

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2019
Testicular Cancer - Pure Seminoma

NCCN Guidelines Index
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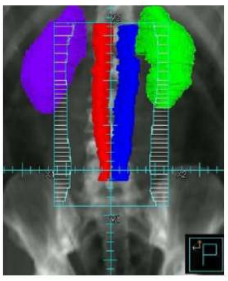
CLINICAL STAGE	PRIMARY TREATMENT[k]
Stage IA, IB	Surveillance for pT1-pT3 tumors (preferred) or Single-agent carboplatin[l,m] (AUC=7 x 1 cycle or AUC=7 x 2 cycles) or RT[n] (20 Gy, preferred or 25.5 Gy)[o]
Stage IS	Repeat elevated serum tumor marker measurement and assess with chest/abdominal/pelvic CT (with contrast) to scan for evaluable disease[p,q]

Target Volumes by Stage (or location)

Figure 1:
Stage I RT Field



[k] Discuss sperm banking prior to chemotherapy or radiation treatment.

ESMO
SPECIAL ARTICLE

ESMO Consensus Conference on testicular germ cell cancer: diagnosis, treatment and follow-up

Risk factors

- Tu size (no deffinite cut off value)
- Stromal invasion in rete testis

- 12% RR - no RF
- 16% RR - either of two RF
- 32% RR - both RF

- Both RF should be considere

8. Who should be offered adjuvant chemotherapy?

Seminoma. In clinical stage I seminoma, several studies have found a low risk of relapse (~5%) in patients without RFs [87, 88, 93]. In these patients, adjuvant chemotherapy will therefore result in over-treatment in ~95% of cases. In patients with a higher risk of relapse, adjuvant chemotherapy remains an option. Adjuvant carboplatin reduces the risk of relapse by ~60% [93], which provides a number-needed-to-treat (NNT) value in the range of 15–20 to prevent one relapse.

Recommendation 8.1: Patients with seminoma and a low risk of relapse should **not** be offered adjuvant chemotherapy.
Level of evidence: III
Strength of recommendation: C
Level of consensus: 91% (30) yes, 6% (2) no, 3% (1) abstain (33 voters)

Recommendation 8.2: In patients with seminoma and a higher risk of relapse, surveillance or adjuvant carboplatin are options.
Level of evidence: III
Strength of recommendation: C
Level of consensus: 91% (30) yes, 6% (2) no, 3% (1) abstain (33 voters)

Recommendation 8.3: In patients with seminoma, patient autonomy should be taken into account following thorough provision of information regarding the pros and cons of the alternative treatment strategies.
Level of evidence: III
Strength of recommendation: C
Level of consensus: 91% (30) yes, 6% (2) no, 3% (1) abstain (33 voters)

Lymphovascular invasion – validated RF

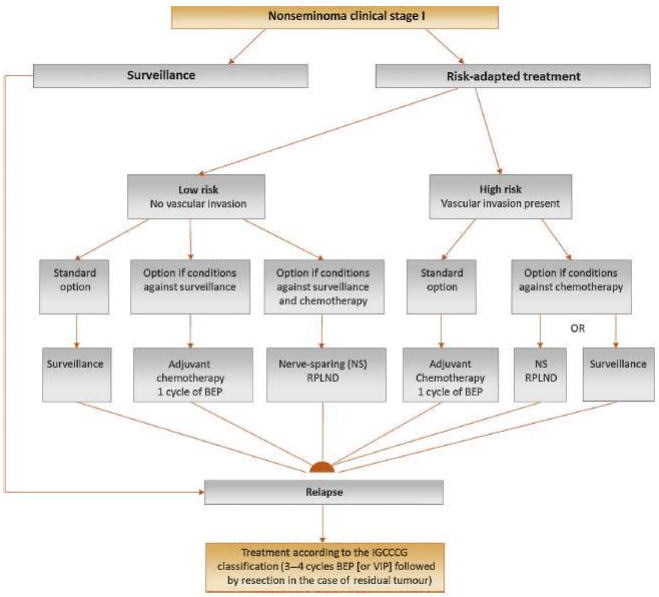


Fig. 1 – Risk-adapted treatment in patients with clinical stage I nonseminoma. All treatment options need to be discussed with individual patients to allow them to make an informed decision as to their further care. BEP = cisplatin, etoposide, bleomycin; CS = clinical stage; IGCCCG = International Germ Cell Cancer Collaborative Group; RLNPD = retroperitoneal lymph node dissection; VIP = etoposide, cisplatin, ifosfamide.

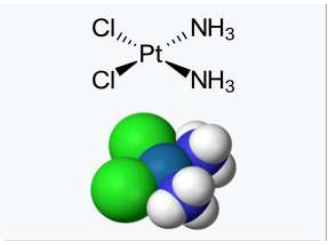
original report

Serum Levels of MicroRNA-371a-3p (M371 Test) as a New Biomarker of Testicular Germ Cell Tumors: Results of a Prospective Multicentric Study

Klaus-Peter Dieckmann, Prof[1,2]; Arlo Radtke, PhD[3]; Lajos Geczi, MD, PhD[4]; Cord Matthies, MD[5]; Petra Anheuser, MD[2]; Ulrike Eckardt, MD[6]; Jörg Sommer, MD[7]; Friedemann Zengerling, MD[8]; Emanuela Trenti, MD[9]; Renate Pichler, PhD[10]; Hanjo Belz, MD[11]; Stefan Zastrow, MD[12]; Alexander Winter, MD[13]; Sebastian Melchior, Prof[14]; Johannes Hammel, MD[14]; Jennifer Kranz, MD[15]; Marius Bolten, MD[16]; Susanne Krege, Prof[17]; Björn Haben, MD[18]; Wolfgang Loidl, MD[19]; Christian Guido Ruf, MD[20]; Julia Heinzelbecker, MD[21]; Axel Heidenreich, Prof[22]; Jann Frederik Cremers, MD[23]; Christoph Oing, MD[24]; Thomas Hermanns, MD[25]; Christian Daniel Fankhauser, MD[25]; Silke Gillessen, MD[26]; Hermann Reichegger, MD[26]; Richard Cathomas, MD[27]; Martin Pichler, Prof[28]; Marcus Hentrich, MD[29]; Klaus Eredics, MD[30]; Anja Lorch, Prof[31]; Christian Wülfing, Prof[1]; Sven Peine, MD[24]; Werner Wosniok, PhD[3]; Carsten Bokemeyer, Prof[24]; and Gazanfer Belge, PhD[3]

miR-371a-3p outperforms the classical biomarkers and represents a highly sensitive and specific new iomarker for TGCC

J Clin Oncol 2019



- Adjuvant chemotherapy
- **Chemotherapy for the metastatic disease**
- Salvage treatment

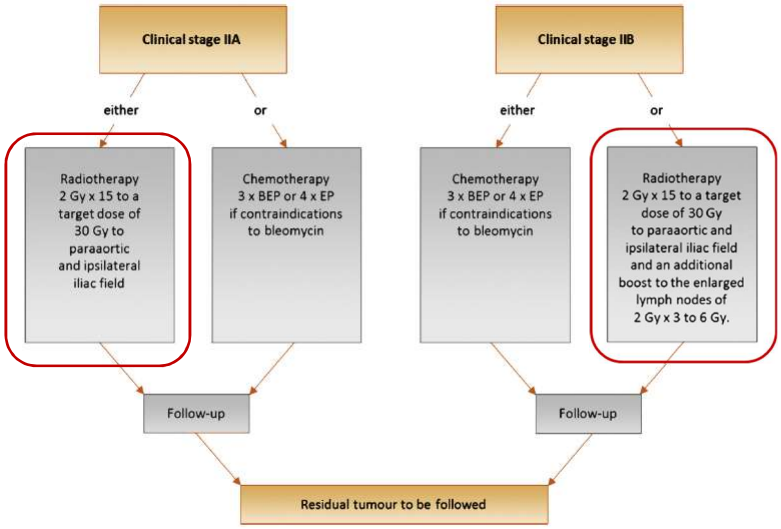


Fig. 2 – Treatment options for patients with clinical stage IIA and IIB seminoma. BEP = cisplatin, etoposide, bleomycin; EP = etoposide, cisplatin.

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2019
Testicular Cancer

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RISK CLASSIFICATION FOR ADVANCED DISEASE (post-orchiectomy)[a]

Risk Status	Nonseminoma	Seminoma
Good Risk	Testicular or retroperitoneal primary tumor and No nonpulmonary visceral metastases and Post-orchiectomy markers- all of: AFP < 1,000 ng/mL hCG < 5,000 iu/L LDH < 1.5 x upper limit of normal	Any primary site and No nonpulmonary visceral metastases and Normal AFP Any hCG Any LDH
Intermediate Risk	Testicular or retroperitoneal primary tumor and No nonpulmonary visceral metastases and Post-orchiectomy markers- any of: AFP 1,000–10,000 ng/mL hCG 5,000–50,000 iu/L LDH 1.5–10 x upper limit of normal	Any primary site and Nonpulmonary visceral metastases and Normal AFP Any hCG Any LDH
Poor Risk	Mediastinal primary tumor or Nonpulmonary visceral metastases or Post-orchiectomy markers- any of: AFP > 10,000 ng/mL hCG > 50,000 iu/L LDH > 10 x upper limit of normal	No patients classified as poor prognosis

Source: Figure 4 from the International Germ Cell Cancer Collaborative Group: International Germ Cell Consensus Classification: A Prognostic Factor-Based Staging System for Metastatic Germ Cell Cancers. J Clin Oncol 1997;15(2):594-603. Reprinted with permission of the American Society of Clinical Oncology.

[a] Markers used for risk classification are post-orchiectomy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

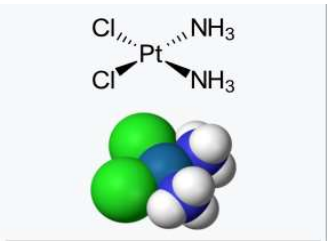
Table 1 | **Serum AFP and hCG levels in GCTs**[22]

GCT histological subtype	AFP	hCG
Yolk sac tumour	++	-
Seminoma	-	±
Embryonal carcinoma	±	±
Choriocarcinoma	-	++
Teratoma	±	-

AFP, α-fetoprotein; GCT, germ cell tumour; hCG, human chorionic gonadotrophin. ++, strongly positive levels; ±, levels may be negative or moderately positive; –, negative levels.

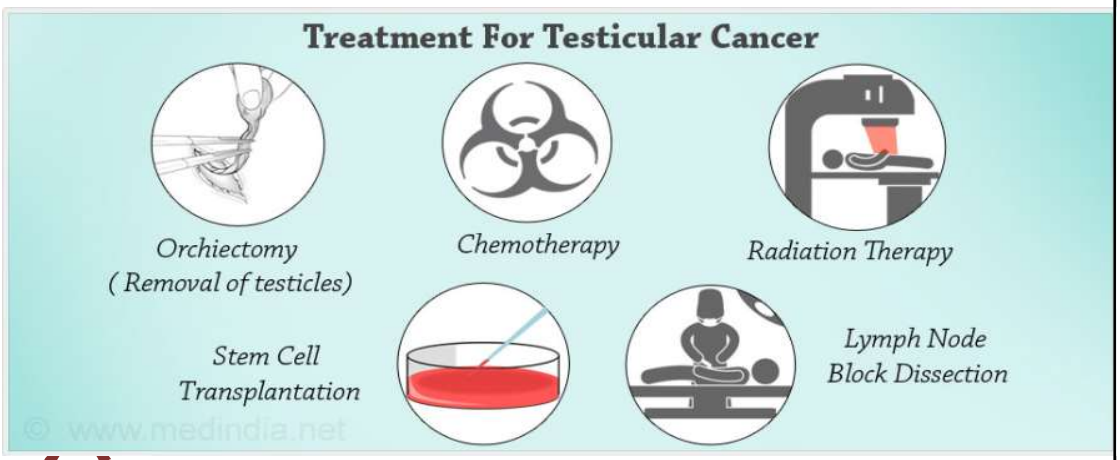
Table 2. Chemotherapy regimens in metastatic seminoma and non-seminoma

BEP[a]	(Repeat cycles every 3 weeks)	
Cisplatin	20 mg/m^2	Day 1–5
Etoposide	100 mg/m^2	Day 1–5
Bleomycin	30 mg	Day 1, 8, 15
EP[b]	(Repeat cycles every 3 weeks)	
Cisplatin	20 mg/m^2	Day 1–5
Etoposide	100 mg/m^2	Day 1–5
VIP/PEI[c]	(Repeat cycles every 3 weeks)	
Cisplatin	20 mg/m^2	Day 1–5
Etoposide	75 mg/m^2	Day 1–5
Ifosfamide	1.2 g	Day 1–5
TIP[d]	(Repeat cycles every 3 weeks)	
Paclitaxel	250 mg/m^2	Day 1
Cisplatin	25 mg/m^2	Day 2–5
Ifosfamide	1.5 g	Day 2–5
VeIP[e]	(Repeat cycles every 3 weeks)	
Vinblastine	0.11 mg/kg	Day 1 + 2
Ifosfamide	1.2 g/m^2	Day 1–5
Cisplatin	20 mg/m^2	Day 1–5
TI-CE[f]	(TI cycles 1–2 every 2 weeks)	
Paclitaxel	200 mg/m^2	Day 1
Ifosfamide	2.0 g	Day 2–4
	(CE cycles 3–5 every 3 weeks)	
Carboplatin	AUC = 7	Day 1–3
Etoposide	400 mg/m^2	Day 1–3
CE[g]	(Two cycles, may be preceded by VeIP)	
Carboplatin	700 mg/m^2	Day 1
Etoposide	750 mg/m^2	Day 1–3



- Adjuvant chemotherapy
- Chemotherapy for the metastatic disease
- Salvage treatment

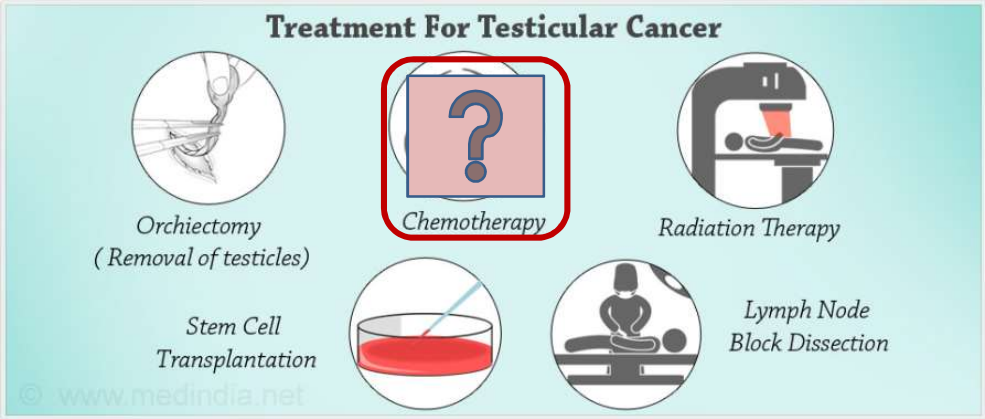
Multidisciplinary treatment



Late relapse of mGCT

recurrent GCT more than 2 years from completion of initial chemotherapy in the absence of a second gonadal primary tumor

evidence of new lesions, or sequentially increasing serum tumour markers (AFP or HCG), more than 2 years after ≥3 cycles of cisplatin-based chemotherapy



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Etoposide	100 mg/m^2	Day 1–5
VIP/PEI[c]	(Repeat cycles every 3 weeks)	
Cisplatin	20 mg/m^2	Day 1–5
Etoposide	75 mg/m^2	Day 1–5
Ifosfamide	1.2 g	Day 1–5
TIP[d]	(Repeat cycles every 3 weeks)	
Paclitaxel	250 mg/m^2	Day 1
Cisplatin	25 mg/m^2	Day 2–5
Ifosfamide	1.5 g	Day 2–5
VeIP	(Repeat cycles every 3 weeks)	
Vinblastine	0.11 mg/kg	Day 1 + 2
Ifosfamide	1.2 g/m^2	Day 1–5
Cisplatin	20 mg/m^2	Day 1–5
TI-CE[f]	(TI cycles 1–2 every 2 weeks)	
Paclitaxel	200 mg/m^2	Day 1
Ifosfamide	2.0 g	Day 2–4
	(CE cycles 3–5 every 3 weeks)	
Carboplatin	AUC = 7	Day 1–3
Etoposide	400 mg/m^2	Day 1–3
CE[g]	(Two cycles, may be preceded by VeIP)	
Carboplatin	700 mg/m^2	Day 1
Etoposide	750 mg/m^2	Day 1–3

Annals of Oncology 24 (Supplement 6): vi125–vi132, 2013

A phase II trial of TIP (paclitaxel, ifosfamide and cisplatin) given as second-line (post-BEP) salvage chemotherapy for patients with metastatic germ cell cancer: a medical research council trial

GM Mead[a,1], MH Cullen[2], R Huddart[3], P Harper[4], GJS Rustin[5], PA Cook[6], SP Stenning[6] and M Mason[7] on behalf of the MRC Testicular Tumour Working Party[8]

[1]Medical Oncology Unit, C Level West Wing, Southampton General Hospital, Southampton SO16 6YD, UK; [2]University Hospital Birmingham NHS Foundation Trust, Birmingham B15 2TH, UK; [3]Royal Marsden Hospital, Sutton SM2 5PT, UK; [4]Guy's Hospital, London SE1 9RT, UK; [5]Mt Vernon Hospital, Harrow HA6 2RN, UK; [6]MRC Clinical Trials Unit, London NW1 2DA, UK; [7]Velindre Hospital, Cardiff CF4 7XL, UK

43 eligible pts (relaps after BEP 1st line for mGCT)
TIP x 4 (G-CSFgiven at the discretion of the investigator)
Primary outcomme measure – response to TIP

Table 2 Response rates, FFS and overall survival

	Response (*N*, %)								
Group	CR	PR MK-ve	Complete resection of viable malignancy CR(S)	IR	Treatment failure/early death	Favourable (CR+PR) response rate (FFR_p) (95% CI)	Favourable (CR+PR+CR(S)) response rate (FFR_c) (95% CI)	1-year FFS rate (95% CI)	1-year overall survival rate (95% CI)
All patients	8 (19%)	18 (42%)	5 (12%)	8 (19%)	4 (9%)	60% (44–75)	72% (56–85)	38% (23–53)	70% (56–84)

CR = complete response; PR = partial response; IR = incomplete response; FFS = failure-free survival; 95% CI = 95% confidence interval.

Table 2 Response rates, FFS and overall survival

	Response (*N*, %)								
Group	CR	PR MK-ve	Complete resection of viable malignancy CR(S)	IR	Treatment failure/early death	Favourable (CR+PR) response rate (FFR_p) (95% CI)	Favourable (CR+PR+CR(S)) response rate (FFR_c) (95% CI)	1-year FFS rate (95% CI)	1-year overall survival rate (95% CI)
All patients	8 (19%)	18 (42%)	5 (12%)	8 (19%)	4 (9%)	60% (44–75)	72% (56–85)	38% (23–53)	70% (56–84)
MSKCC good risk	7 (27%)	12 (46%)	2 (8%)	3 (12%)	2 (8%)	73% (52–88)	81% (61–93)	43% (23–63)	81% (64–98)
MSKCC poor risk	1 (6%)	6 (35%)	3 (18%)	5 (29%)	2 (12%)	41% (18–67)	59% (33–82)	29% (8–51)	53% (29–77)

CR = complete response; PR = partial response; IR = incomplete response; FFS = failure-free survival; 95% CI = 95% confidence interval.

Table 3. Patient Characteristics Found to be Predictive of Survival in the Univariate Analysis

Characteristic	No. of Patients	No. Alive	Median Survival (months)	*P*
All patients	58	17	11	NA
Primary tumor site				.04
Gonadal	51	16	12	
Extragonadal	7	1	3	
Retroperitoneal metastases				.08
No	21	3	9	
Yes	37	14	12	
Prior best response				.04
Incomplete	36	8	8	
Complete	22	9	24	
Refractory status[10]				.04
Absolute refractory	12	3	7	
Refractory	21	3	7	
Relapsed	25	11	24	
Pretreatment HCG continuous variable	58	NA	NA	.03

Abbreviation: NA, not applicable.

Figure 3 Survival, all eligible patients.

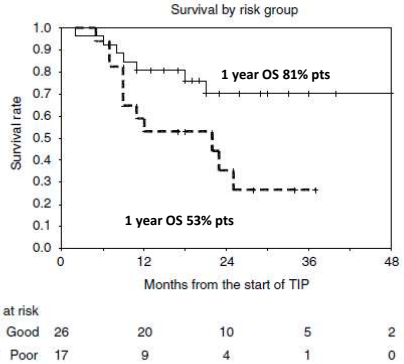


Figure 4 Survival by risk group.

British Journal of Cancer (2005) 93(2), 178 – 184

Salvage therapy of testicular cancer

High dose chemotherapy

ORIGINAL ARTICLE

High-Dose Chemotherapy and Stem-Cell Rescue for Metastatic Germ-Cell Tumors

Lawrence H. Einhorn, M.D., Stephen D. Williams, M.D., Amy Chamness, B.A., Mary J. Brames, R.N., Susan M. Perkins, Ph.D., and Rafat Abonour, M.D.

Retrospective study
184 pts
- **2nd line (135)**
- **3rd or subsequent lines (49)**

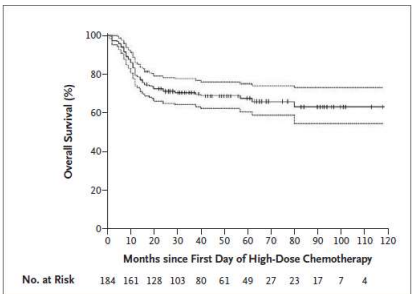


Figure 1. Kaplan–Meier Estimates of Overall Survival.
The top and bottom lines show the 95% confidence interval.

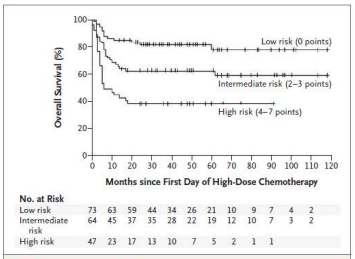


Figure 2. Disease-free Survival.
The prognostic scoring algorithm, based on the three-variable model, assigned a score of 3 points for third-line chemotherapy, 2 points for platinum refractoriness, and 2 points for advanced International Germ Cell Cancer Collaborative Group stage. High scores indicated a low probability of disease-free survival.

Table 3. Results of Multivariate Cox Proportional-Hazards Analysis and Prognostic Score.*

Prognostic Variable	Hazard Ratio (95% CI)	P Value	β Regression Coefficient	Prognostic Score†
Third-line or subsequent chemotherapy	2.19 (1.35–3.56)	0.002	0.78	3
Platinum-refractory disease	1.74 (1.01–3.00)	0.05	0.55	2
IGCCCG high-risk stage	1.67 (1.00–2.78)	0.05	0.51	2

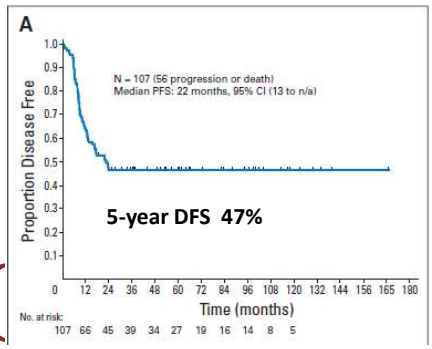
* The hazard ratio is for disease progression. IGCCCG denotes International Germ Cell Cancer Collaborative Group.
† The score was calculated by dividing the regression coefficient by 0.51, multiplying by 2.0, and rounding to the nearest whole number.

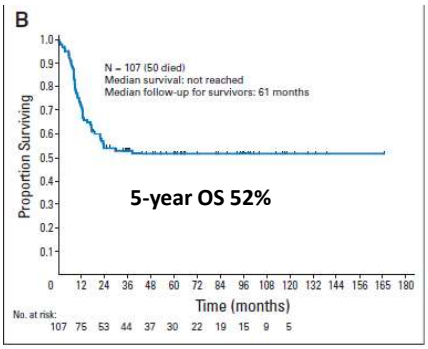
TI-CE High-Dose Chemotherapy for Patients With Previously Treated Germ Cell Tumors: Results and Prognostic Factor Analysis

Darren R. Feldman, Joel Sheinfeld, Dean F. Bajorin, Patricia Fischer, Stefan Turkula, Nicole Ishill, Sujata Patil, Manjit Bains, Lilian M. Reich, George J. Bosl, and Robert J. Motzer

Retrospective analysis: 107 pts
Unfavorable prognostic features (incomplete response to 1st line, relapse/incomplete response to cisplatin/ifosfamide based CDCT salvage, ekstragonadal primary)

- **m follow-up: 61 months**
- **50% CR and 8% PR neg TM;**
- **No relapses occurred after 2 years.**
- **24 of primary mediastinal nonseminomatous GCTs are continuously disease free**





Original article

Annals of Oncology 16: 1152–1159, 2005
doi:10.1093/annonc/mdi228
Published online 31 May 2005

IT-94 trial

A randomised trial of high-dose chemotherapy in the salvage treatment of patients failing first-line platinum chemotherapy for advanced germ cell tumours

J.-L. Pico[1], G. Rosti[2], A. Kramar[3]*, H. Wandt[4], V. Koza[5], R. Salvioni[6], C. Theodore[1], G. Lelli[7], W. Siegert[8], A. Horwich[9], M. Marangolo[2], W. Linkesch[10], G. Pizzocaro[6], H.-J. Schmoll[11], J. Bouzy[1], J.-P. Droz[12] & P. Biron[12], for the Genito-Urinary Group of the French Federation of Cancer Centers (GETUG-FNCLCC), France and the European Group for Blood and Marrow Transplantation (EBMT)

February 1994 and September 2001, 280 patients from 43 institutions in 11 countries
- **arm A: four cycles of cisplatin, ifosfamide and etoposide (or vinblastine)**
- **arm B: three such cycles followed by high-dose carboplatin, etoposide and cyclophosphamide (CarboPEC) with haematopoietic stem cell support**

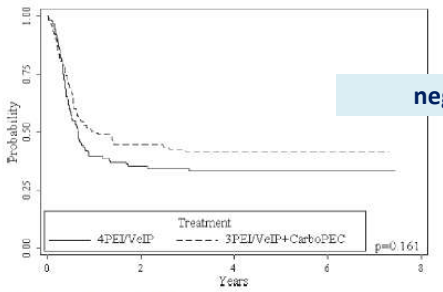


Figure 1. Event-free survival.

negative study

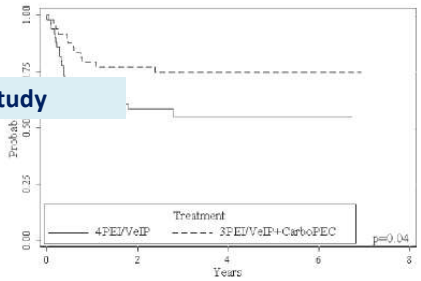
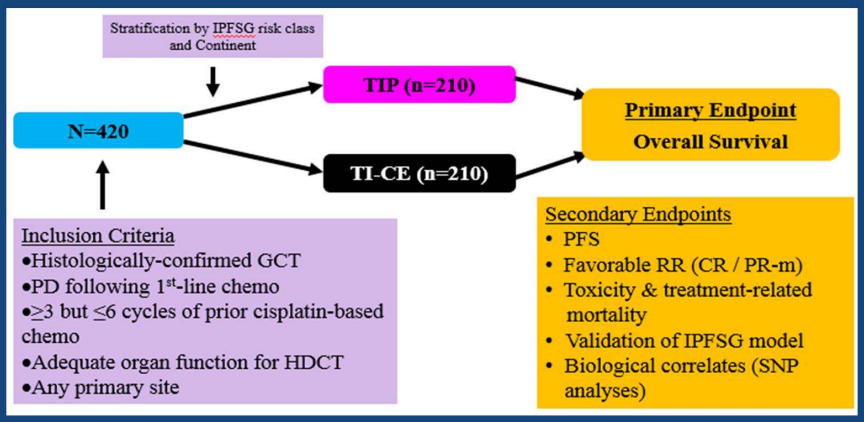


Figure 2. Disease-free survival from time of overall treatment evaluation among patients in complete remission.

TIGER: international, prospective Phase III trial



Sponsor: Alliance (USA, **D. Feldman**), EORTC (Europe, **T. Powles**), Movember

Presented By Anja Lorch at 2018 ASCO Annual Meeting

Table 4. Relapsed GCC: International Prognostic Factors Study Group classification [1]

Parameter	Score points			
	0	1	2	3
Primary site	Gonadal	Extragonadal	-	Mediastinal non-seminoma
Prior response	CR/PRm-	PRm+/SD	PD	-
PFI, months	>3	≤3	-	-
AFP salvage	Normal	≤1000	>1000	-
hCG salvage	≤1000	>1000	-	-
Score sum (values from 0 to 10)				
Regroup score sum into categories: (0) = 0; (1 or 2) = 1; (3 or 4) = 2; (5 or more) = 3				
Add histology score points: pure seminoma = -1; non-seminoma or mixed tumours = 0				
Final prognosis score (-1 = very low risk; 0 = low risk; 1 = intermediate risk; 2 = high risk; 3 = very high risk)				

AFP, α-fetoprotein; CR, complete remission; GCC, germ cell cancer; hCG, human chorionic gonadotrophin; PD, progressive disease; PFI, progression-free interval; PRm-, partial remission, negative markers; PRm+, partial remission, positive markers; SD, stable disease.

Annals of Oncology 29: 1658–1686, 2018 (supplements)

insufficient evidence to determine whether CDCT or HDCT produces superior outcomes as first-salvage chemotherapy → either CDCT or HDCT acceptable options for first-salvage chemotherapy

Table 3. 'Third-line' regimens used for second or subsequent salvage treatment

Single agent

Regimen	Dose	Schedule	Reference
Gemcitabine	1000 mg/m^2	d1, 8, 15 q3w	[241]
	1200 mg/m^2	d1, 8, 15 q3w	[242]
Oxaliplatin	60 mg/m^2 or 85 mg/m^2	d1, 15 q4w	[243]
Paclitaxel	170 mg/m^2	d1, q3w	[244]
	225 mg/m^2	d1, q3w	[245]
	250 mg/m^2	d1, q3w	[246]
	250 mg/m^2	d1, q3w	[247]
Oral etoposide	50 mg/m^2/day	Continuously	[248]

Two drug combinations

Regimen	Dose	Schedule	Reference
Gemcitabine	1000 mg/m^2 or 1250 mg/m^2	d1, 8 q3w	[249–251]
Oxaliplatin	130 mg/m^2	d1, q3w	
Gemcitabine	1000 mg/m^2	d1, 8, 15 q4w	[252, 253]
Paclitaxel	100 mg/m^2		

Three drug combinations

Regimen	Dose	Schedule	Reference
Gemcitabine	800 mg/m^2	d1, 8 q3w	[254]
Oxaliplatin	130 mg/m^2	d1, q3w	
Paclitaxel	80 mg/m^2	d1, 8 q3w	
Gemcitabine	800 mg/m^2	d1, 8 q3w	[255]
Cisplatin	50 mg/m^2	d1, 8 q3w	
Paclitaxel	80 mg/m^2	d1, 8 q3w	

d, day; q3w, every 3 weeks; q4w, every 4 weeks.

Annals of Oncology 29: 1658–1686, 2018

Palliative treatment in GCT

Cancer Treatment Reviews

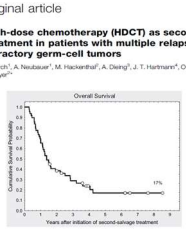
Tumour Review

Palliative treatment of germ cell cancer

Christoph Oing[a,1], Patrizia Giannatempo[b,1], Friedemann Honecker[c], Karin Oechsle[a], Carsten Bokemeyer[a], Jörg Beyer[d,*]

original article

High-dose chemotherapy (HDCT) as second-salvage treatment in patients with multiple relapsed or refractory germ-cell tumors



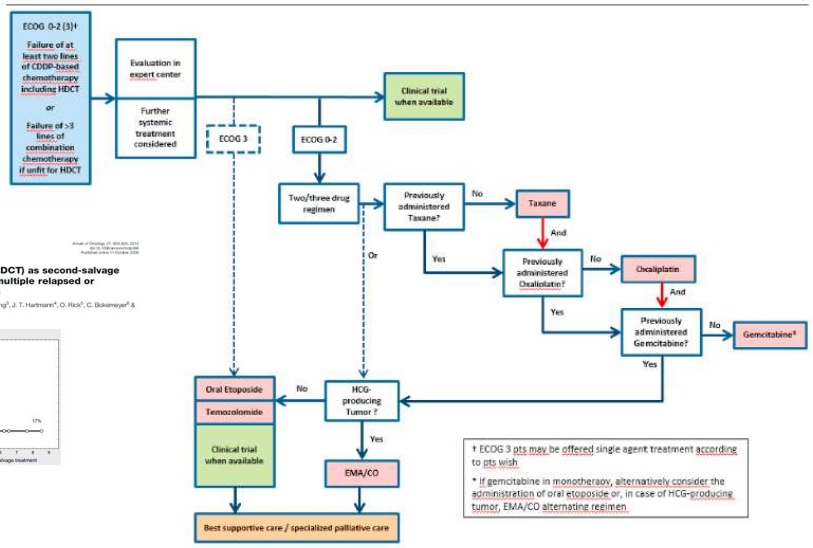


Fig. 1. Treatment algorithm for selection of palliative treatments.

Phase I / II studies			
Kollmansberger C	trastuzumab	HER2/neu expressing GCT	Ann Oncol 1999
Rick O	talidomid	platinum refrac	Eur J Cancer 2006
Feldman DR	sunitinib	relapse actory GCT	Invest New Drugs 2010
Feldman DR	tivantinib	ed or refractory	Invest New Drugs 2013
Einhorn LH	imatinibmesila	CTX refractory GCT expressing KIT	J Clin Oncol 2006
Necchi A	pazor	relapsed or refractory GCT	Ann Oncol 2017
Fenner M	limus	multiply relapsed GCT	Journal of Cancer Research and Clinical Oncology, 2018
Adra N	pembrolizumab	multiply relapsed GCT, no other treatment option	Annals of Oncology, 2018

negative results

RESEARCH

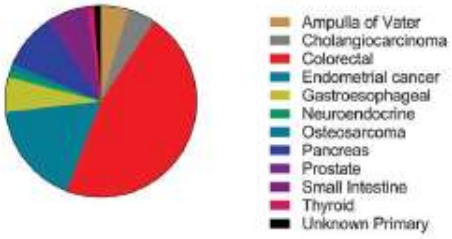
CANCER BIOMARKERS

Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade

Le et al., Science 357, 409–413 (2017)

the genomes of cancers deficient in MMR contain exceptionally high numbers of somatic mutations

⟹ sensitivity to immune checkpoint blockade



- **12 different tumor types**

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2019
Testicular Cancer - Nonseminoma

NCCN Guidelines Index
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RECURRENCE[qq] — **THIRD-LINE THERAPY[kk,ss]**

Prior chemotherapy

- Prior first- and second-line conventional dose chemotherapy → Clinical trial (preferred) or High-dose chemotherapy[tt]
- Prior high-dose chemotherapy → Clinical trial (preferred) or Conventional dose salvage chemotherapy[tt] or Consider surgical salvage if solitary site or **MSI/MMR testing if progression after high-dose chemotherapy or third-line therapy[rr]**
- Late relapse (recurrence >2 years after completion of second-line chemotherapy) → Surgical salvage, if resectable (preferred) or Chemotherapy[tt]
  - Conventional-dose therapy
  - High-dose chemotherapy (if not previously received)

[kk] To assess response after treatment, CT with contrast of chest/abdominal/pelvic and any other sites of disease is recommended.
[qq] It is preferred that patients with recurrent nonseminoma be treated at centers with expertise in the management of this disease.
[ss] Includes best supportive care.
[tt] See Third-Line Chemotherapy Regimens for Metastatic Germ Cell Tumors (TEST-G).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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NCCN Guidelines Version 1.2019
Testicular Cancer

NCCN Guidelines Index
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Discussion

THIRD-LINE CHEMOTHERAPY REGIMENS FOR METASTATIC GERM CELL TUMORS[a]

High-Dose Chemotherapy NOT Previously Received

Preferred Regimens

High-Dose Chemotherapy

- Carboplatin 700 mg/m² (body surface area) IV
  Etoposide 750 mg/m² IV
  Administer 5, 4, and 3 days before peripheral blood stem cell infusion for 2 cycles[1]
- Paclitaxel 200 mg/m² IV over 24 hours on Day 1
  Ifosfamide 2000 mg/m² over 4 hours with mesna protection on Days 2–4
  Repeat every 14 days for 2 cycles followed by
  Carboplatin AUC 7–8 IV over 60 minutes on Days 1–3
  Etoposide 400 mg/m² IV on Days 1–3
  Administer with peripheral blood stem cell support at 14- to 21-day intervals for 3 cycles[2]

Other Recommended Regimens[b]

- Gemcitabine/paclitaxel/oxaliplatin[3]
- Gemcitabine/oxaliplatin[4-6]
- Gemcitabine/paclitaxel[7,8]
- Etoposide (oral)[9]

Useful in Certain Circumstances[b]

- Pembrolizumab (for MSI-H/dMMR tumors)[10,11]

High-Dose Chemotherapy Previously Received

Preferred Regimens[b]

- Gemcitabine/paclitaxel/oxaliplatin[3]
- Gemcitabine/oxaliplatin[4-6]
- Gemcitabine/paclitaxel[7,8]
- Etoposide (oral)[9]

Useful in Certain Circumstances[b]

- Pembrolizumab (for MSI-H/dMMR tumors)[10,11]

[a] If VIP or TIP received as second-line therapy, high-dose chemotherapy is the preferred third-line option.
[b] See references on TEST-G (2 of 2) for dosing.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

ESMO
Annals of Oncology 29: 209–214, 2018
doi:10.1093/annonc/mdx680
Published online 17 October 2017

ORIGINAL ARTICLE

Phase II trial of pembrolizumab in patients with platinum refractory germ-cell tumors: a Hoosier Cancer Research Network Study GU14-206

N. Adra[1*], L. H. Einhorn[1], S. K. Althouse[2], N. R. Ammakkanavar[1], D. Musapatika[3], C. Albany[1], D. Vaughn[4] & N. H. Hanna[1]

- **Single arm phase II trial investigating pembrolizumab 200mg i.v. Q3 weeks until disease progression**
- **Primary end point ORR using immune-related response criteria**

- **Patients with relapsed GCT and no curable options**
- **12 patients enrolled, median age 38 years,**
  - **all patients had nonseminoma,**
  - **six patients had late relapse (>2 years)**
- **2 patients had positive PD-L1 staining**
- **No CR or PR observed**
- **2 pts radiographic SD (28 and 19 weeks),**
  - **both had continued rising AFP level despite radiographic stability and had negative PD-L1 staining**

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